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(19)

(54) SUBSTITUTED 16,17,18,19,20-PENTANOR-PROSTAGLANDINS

(71) We, PFIZER INC., a Corporation organized under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to certain novel analogs of the naturally occurring prostaglandins and to various novel intermediates and reagents useful in their preparation. In particular it relates to novel 16, 17, 18, 19, 20-pentanor-prostaglandins.

The prostaglandins are C-20 unsaturated fatty acids which exhibit diverse physiological effects. For instance, the prostaglandins of the E and A series are potent vasodilators (Bergstrom, *et. al., Acta Physiol. Scand. 64:332—33, 1965 and Bergstrom, et al., Life Sci.* 6:449—455, 1967) and lower systemic arterial blood pressure (vasodepression) on intravenous administration (Weeks and King, *Federation Proc.* 23:327, 1964; Bergstrom, *et. al.*, 1965, *op. cit.*; Carlson, *et al., Acta Med. Scand.* 183:423—430, 1968; and Carlson, *et al., Acta Physiol. Scand.* 75:161—169, 1969). Another well known physiological action for PGE_1 and PGE_2 is as a bronchodilator (Cuthbert, *Brit. Med. J.* 4:723—726, 1969).

Still another important physiological role for the natural prostaglandins is in connection with the reproductive cycle. PGE_2 is known to possess the ability to induce labor (Karim, *et. al., J. Obstet Gynaec. Brit. Cwlth.* 77:200—210, 1970), to induce therapeutic abortion (Bygdeman, *et. al., Contraception, 4,* 293 (1971) and to be useful for control of fertility (Karim, *Contraception, 3,* 173 (1971)). Patents have been obtained for several prostaglandins of the E and F series as inducers of labor in mammals (Belgian Patent 754,158 and West German Patent 2,034,641), and on PGF_1, F_2, and F_3 for control of the reproductive cycle (South African Patent 69/6089).

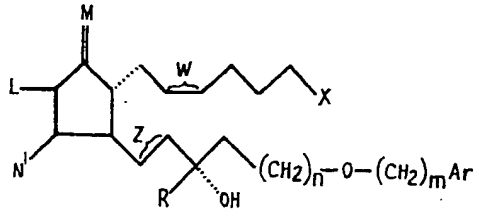
Still other known physiological activities for PGE_1 are in the inhibition of gastric acid secretion (Shaw and Ramwell, In: *Worcester Symp. on Prostaglandins,* New York, Wiley, 1968, p. 55—64) and also of platelet aggregation (Emmons, *et al.*, Brit. Med. J. 2:468—472, 1967).

It is now known that such physiological effects will be produced *in vivo* for only a short period, following the administration of a prostaglandin. A substantial body of evidence indicates that the reason for this rapid cessation of activity is that the natural prostaglandins are quickly and efficiently metabolically deactivated by β-oxidation of the carboxylic acid side-chain and by oxidation of the 15α-hydroxyl group (Anggard, *et al., Acta. Physiol. Scand., 81,* 396 (1971) and references cited therein).

It was, of course, considered desirable to create analogs of the prostaglandins

which would have physiological activities equivalent to the natural compounds, but in which the selectivity of action and the duration of the activity would be increased. Increased selectivity of action would be expected to alleviate the severe side effects, particularly gastrointestinal side effects, frequently observed following systemic administration of the natural prostaglandins (see *Lancet*, 536, 1971).

An aspect of the invention is concerned with a process for preparing a compound of the formula:



...I

and its C_{15} epimer;
wherein

Ar is phenyl, 3,4-dimethoxyphenyl, 3,4-methylene-dioxyphenyl, 3,4,5-trimethoxyphenyl; α- or β-naphthyl or mono-substituted phenyl wherein said substituent is halogen, trifluoromethyl, phenyl, lower alkyl or lower alkoxy; wherein "lower" herein refers to groups containing 1 to 6 carbon atoms;

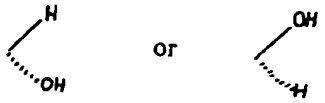
R is hydrogen or lower alkyl;

n and m are each O or integers from 1 to 3 with the proviso that the sum of n and m does not exceed 3;

W is a single bond or *cis* double bond;

Z is a single bond or *trans* double bond;

M is oxo,



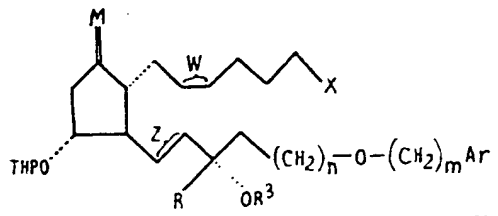
N' and L when taken together form a single bond, or

N' is α-hydroxyl and L is hydrogen with the proviso that when N' and L together form a single bond M is oxo;

X is *p*-phenylphenoxycarbonyl; 5-tetrazolyl; or

wherein R" is alkanoyl having from 2—10 carbon atoms or cycloalkanoyl having from 4 to 8 carbon atoms; aroyl or substituted aroyl of from 7 to 11 carbon atoms wherein said substituent is methyl, halogen or methoxy; alkylsulfonyl of from 1 to 7 carbon atoms; arylsulfonyl or substituted arylsulfonyl wherein said substituent is methyl, halogen or methoxy; the lower alkanoates, formates or benzoates of any free hydroxyl groups at the C_9-, C_{11}- and C_{15}-positions, which comprises:—

a) when N' is α-hydroxy and L is hydrogen and Ar, N, m, M, W, X and Z are as defined above, hydrolysing with an acid a compound of Formula IIC:—

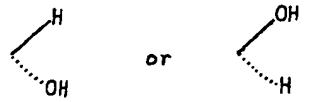


IIc

or the C_{15} epimer thereof, wherein Ar, n, m, W, Z and X are as defined above THP is 2-tetrahydropyranyl, and R^3 is hydrogen or THP, with the proviso that when R^3 is hydrogen M is oxo;

b) when N′ and L, when taken together form a single bond, M is oxo and Ar, n, m, R, W, X and Z are as defined above, reacting a compound of Formula I, above, wherein N′ is α-hydroxy and L is hydrogen, M is oxo and Ar, n, m, R, W, X and Z are as defined above, with an acidic dehydrating agent;

c) when N′ is α-hydroxy and L is hydrogen, M is



and Ar, n, R, W and Z are as defined above, reducing a compound of the Formula I, above, wherein N′ is α-hydroxy and L is hydrogen, M is oxo, Ar, n, m, R, W, X and Z are as defined above, with a carbonyl reducing agent which does not react with ester or carboxamide groups or carbon to carbon double bonds, and, if desired, separating the 9α- and 9β-isomers;

d) when N′ is α-hydroxy, L is hydrogen, Ar, R, n, m, M and X are as defined above, and W and Z are single bonds, catalytically hydrogenating a compound of Formula I, above, wherein Ar, R, n, m, M and X are as defined above, W is a single bond or *cis* double bond when Z is a *trans* double bond and Z is a single bond when W is a *cis* double bond;

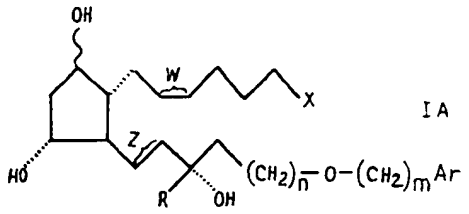
e) when N′ is α-hydroxy, L is hydrogen, Ar, R, n, m, X and M are as defined above, W is a single bond and Z is a *trans* double bond, selectively hydrogenating a compound of Formula I, wherein Ar, R, n, m, X and M are as defined above and W is a *cis* double bond and Z is a *trans* double bond;

f) when X is *p*-phenylphenoxycarbonyl, Ar, R, n, m, L, N′, W and Z are as defined above, reacting a compound of formula I wherein X is —COOH with *p*-phenylphenol;

g) when X is

wherein R″ is as defined above, M, Ar, R, n, m, L, N′, W and Z are as defined above, reacting a compound of Formula I above wherein X is COOH with an isocyanate of the formula R″NCO, wherein R″ is as defined above, and hydrolysing the compound thus obtained; and if desired, preparing the 9α- or 9β-, 11α- and 15α- lower alkanoates, formates or benzoates of the free hydroxy groups at the C_9, C_{11} and C_{15} positions by reacting said compounds with the appropriate acylating agents.

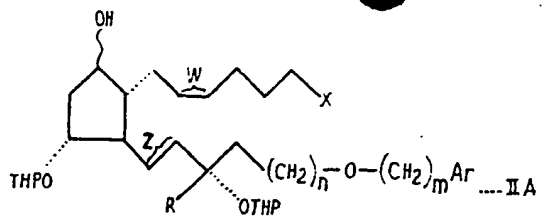
More specifically, an aspect of the invention resides in a process for preparing a compound of the formula:—



IA

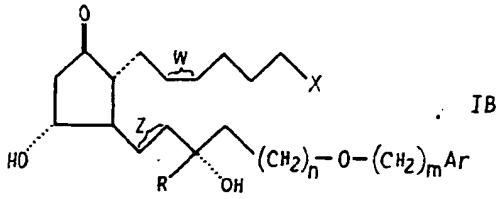
and its C_{15} epimer, wherein Ar, R, n, m, W, Z and X are as hereinbefore defined, the tri(lower alkanoates), triformates or tribenzoates of the free hydroxy groups at the C_9-, C_{11}- and C_{15}-positions, which comprises:—

a) hy[illegible]sing with an acid a compound of Formu[illegible]A:—



or its C_{15} epimer, wherein Ar, R, n, m, W, Z, X and THP are as hereinbefore defined;

b) reducing a compound of the formula:



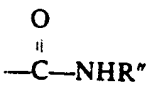
IB

or its C_{15} epimer, wherein Ar, n, m, R, W, X and Z are as defined above, with a carbonyl reducing agent which does not react with ester or carboxamide groups or carbon to carbon double bonds, and then separating the 9α- and 9β-isomers;

c) catalytically hydrogenating a compound of Formula IA, above, wherein Ar, R, n, m and X are as defined above, W is a single bond or *cis* double bond when Z is a *trans* double bond and Z is a single bond when W is a *cis* double bond, to a compound of Formula IA, above, wherein Ar, n, M and X are as defined above and W and Z are single bonds;

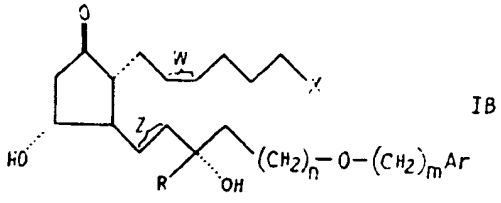
d) when X is *p*-phenylphenoxycarbonyl, Ar, R, n, m, L, N', W and Z are as defined above, reacting a compound of formula I wherein X is —COOH with *p*-phenylphenol;

e) when X is



wherein R" is as defined above, M, Ar, R, n, m, L, N', W and Z are as defined above, reacting a compound of formula I above wherein X is COOH with an isocyanate of the formula R"NCO, wherein R" is as defined above, and hydrolysing the compound thus obtained; and, if desired, preparing the 9α- or 9β-, 11α- and 15α-tri(lower alkanoates), triformates or tribenzoates of the free hydroxy groups at the C_9, C_{11} and C_{15} positions by reacting said compounds with the appropriate acylating agents.

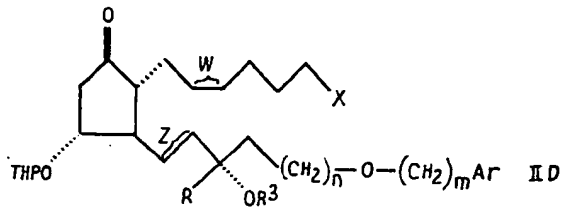
More specifically, an aspect of the invention resides in a process for preparing a compound of the formula:—



IB

and its C_{15} epimer, wherein Ar, R, n, m, W, Z and X are as defined above, the di(lower alkanoates), diformates or dibenzoates of the free hydroxy groups at the C_{11}- and C_{15}-positions which comprises:—

a) hydrolysing with an acid, a compound of Formula IID:—



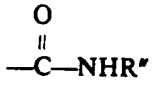
IID

or its C_{15} epimer wherein Ar, R, m, n, W, Z, X, R^3 and THP are as defined above;

b) catalytically hydrogenating a compound of Formula IB, above, wherein Ar, X, R, m and n are as defined above W is a single bond or a *cis* double bond when Z is a *trans* double bond and Z is a single bond when W is a *cis* double bond, to afford a compound of Formula IB wherein Ar, X, m, n, and R are as defined above and W and Z are single bonds;

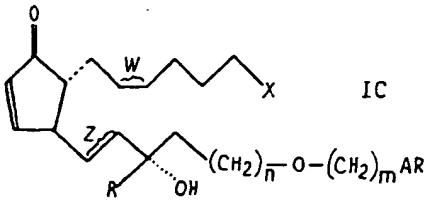
c) when X is *p*-phenylphenoxycarbonyl, Ar, R, n, m, L, N', W and Z are as defined above, reacting a compound of formula I wherein X is —COOH with *p*-phenylphenol;

d) when X is



wherein R″ is as defined above, M, Ar, R, n, m, L, N', W and Z are as defined above, reacting a compound of formula I above wherein X is COOH with an isocyanate of the formula R″NCO, wherein R″ is as defined above, and hydrolysing the compound thus obtained, and, if desired, preparing the di(lower alkanoates), diformates or dibenzoates of the free 11- and 15-hydroxy groups by reacting said compounds with the appropriate acylating agents.

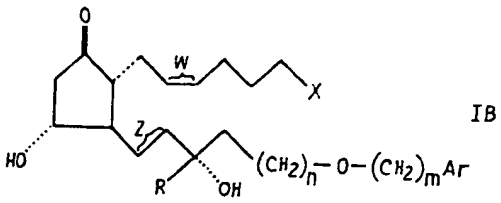
More specifically, an aspect of the invention resides in a process for preparing a compound of the formula:—



IC

and its C_{15} epimer, wherein Ar, R, m, n, W, X and Z are as hereinbefore defined, the lower alkanoates, formates or benzoates of the C_{15}-hydroxy group, which comprises:—

a) treating a compound of Formula IB,



IB

or its C_{15} epimer wherein Ar, R, m, n, W, X and Z are as defined above, with an acid;

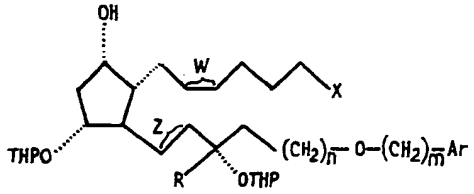
b) when X is *p*-phenylphenoxycarbonyl, Ar, R, n, m, L, N', W and Z are as defined above, reacting a compound of formula I wherein X is —COOH with *p*-phenylphenol;

c) when X is

$$-\overset{\overset{O}{\|}}{C}-NHR''$$

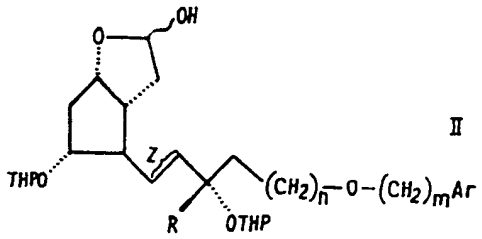
wherein R" is as defined above, M, Ar, R, n, m, L, N', W and Z are as defined above, reacting a compound of formula I above wherein X is COOH with an isocyanate of the formula R"NCO wherein R" is as defined above, and hydrolysing the compound, thus obtained; and, if desired, preparing the C_{15}-lower alkanoates, formates or benzoates by reacting said compound with the appropriate acylating agents.

Within the ambit of the invention is a process for preparing a compound of the formula:—



. . IIAA

and the C_{15} epimer thereof wherein Ar, R, m, n, W, Z, X and THP are as hereinbefore defined which comprises reacting a compound of Formula II:—



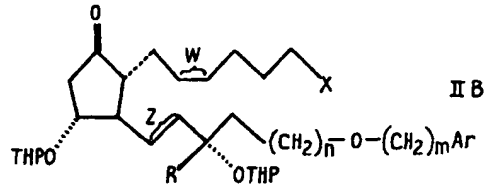
II

or the C_{15} epimer thereof, wherein Ar, R, n, m, Z and THP are as defined above, with an ylide of the formula

$$(C_6H_5)_3P{=}CH{-}CH_2{-}CH_2{-}CH_2{-}X$$

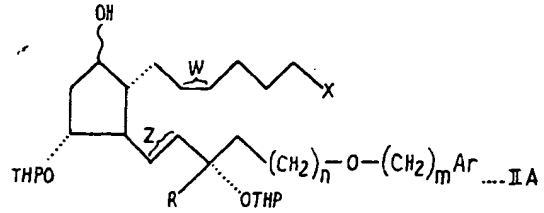
wherein X is as defined above, with the proviso that when X is *p*-phenylphenoxycarbonyl, the compound of Formula II is first reacted with an ylide $(C_6H_5)_3{-}P{=}CH{-}CH_2{-}CH_2{-}CH_2{-}CO_2H$ and the resulting compound esterified with *p*-phenylphenol, to afford a compound of Formula IIA wherein Ar, R, n, m, X, Z and THP are as defined above and W is a *cis* double bond, and, when required, subsequently hydrogenating a compound of Formula IIA above, wherein Ar, R, m, X, n, and THP are as defined above, W is a *cis* double bond, and Z is a *trans* double bond, to form a compound of formula II above wherein Ar, R, m, n and THP are as defined above and W and Z are single bonds; selectively hydrogenating a compound of Formula IIA above wherein Ar, R, m, n and THP are as defined above, W is a *cis* double bond and Z is a *trans* double bond, to form a compound of Formula IIA, wherein Ar, R, m, X, n and THP are as defined above, W is a single bond and Z is a *trans* double bond.

Further, an aspect of the invention is concerned with a process for preparing a compound of the formula:—



IIB

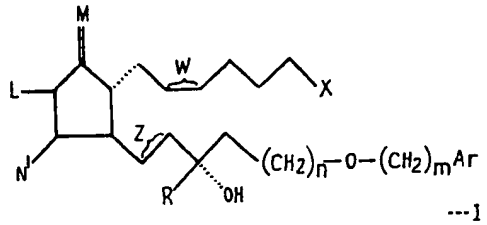
and the C_{15} epimer thereof; wherein Ar, R, m, n, W, Z, X and THP are as hereinbefore defined, which comprises reacting a compound of Formula IIA:



...IIA

wherein Ar, R, n, m, X, W and Z are as defined above with chromic acid in aqueous sulfuric acid and acetone.

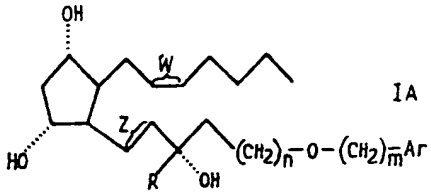
In general, the present invention provides a compound of the formula:



---I

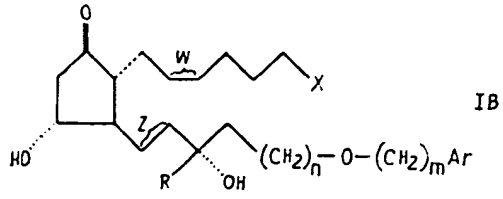
and its C_{15} epimer; wherein Ar, R, n, m, W, Z, M, L, N' and X are as hereinbefore defined, and the lower alkanoates, formates and benzoates of the hydroxy groups at the C_9-, C_{11}- and C_{15}-positions.

More specifically, the present invention provides compounds of the Formulae:



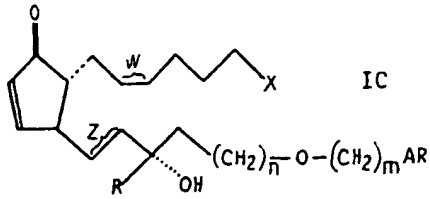
IA

and its C_{15} epimer,



IB

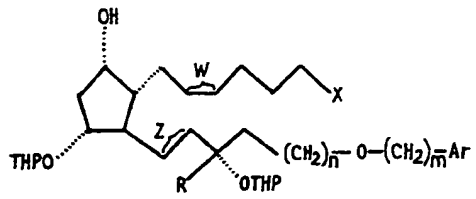
and its C_{15} epimer, and



IC

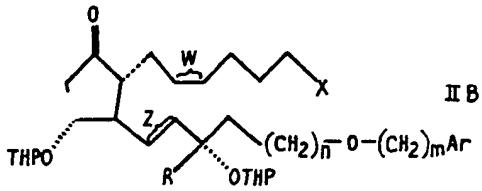
and its C_{15} epimer, wherein Ar, m, n, R, X, Y and Z are as defined above.

Additionally, the present invention provides a compound of the formula:—



IIA

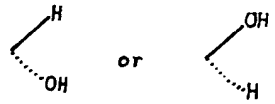
and the C_{15} epimer thereof wherein Ar, R, n, m, W, Z, X and THP are as hereinbefore defined and a compound of the formula:—



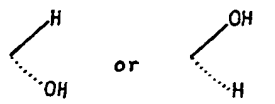
IIB

and the C_{15} epimer thereof; wherein Ar, R, m, n, W, Z, X and THP are as hereinbefore defined.

Preferred compounds are those of Formula I wherein M is oxo, L is a single bond, and N' is α-hydroxy, n and m are each O, Ar is phenyl, W is a *cis* double bond, Z is a *trans* double bond and its C_{15} epimer; wherein n and m are each O, Ar is phenyl, M is



N' is α-hydroxy, L is hydrogen, W is a *cis* double bond and Z is a *trans* double bond, wherein n is O, m is O, Ar is phenyl, M is oxo, N' and L together form a single bond, W is a *cis* double bond and Z is a *trans* double bond, wherein n is O, m is 1, Ar is phenyl, M is oxo, N' is α-hydroxy, L is hydrogen W is a *cis* double bond and Z is a *trans* double bond, wherein n is O, m is 1, Ar is phenyl, M is



N' is α-hydroxy, L is hydrogen, W is a *cis* double bond and Z is a *trans* double bond.

Additional preferred compounds are those of Formula IA wherein n and m are each O and Ar, R, W, Z and X are as hereinbefore defined, wherein n and m are each 1 and Ar, R, W, Z and X are as hereinbefore defined, 1 - (5 - tetrazolyl) - 9α,11α,15α - trihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadiene, *N* - methanesulfonyl - 9α,11α,15α - trihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide, *N*-methanesulfonyl - 9α,11α,15α - trihydroxy - 16 - *m* - methoxyphenoxy - 17,18,19,20 - tetranor - *cis* - 5 - trans - 13 - prostadienamide, and *N* - acetyl - 9α,11α,15α - trihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide.

Further preferred compounds are those of Formula IB wherein n and m are each O and Ar, R, W, Z, and X are as hereinbefore defined, wherein n and m are each 1 and Ar, R, W, Z and X are as hereinbefore defined, *N* - acetyl - 11α,15α - dihydroxy - 9 - oxo - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide, *N* - acetyl - 11α,15α - dihydroxy - 9 - oxo - 16 - *m* - methyoxy - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide, 1 - (5 - tetrazolyl) - 11α,15α - dihydroxy - 9 - oxo - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadiene and *N* - methanesulfonyl - 11α,15α - dihydroxy - 9 - oxo - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadien - amide.

More specifically, preferred compounds are 16 - phenoxy - 17,18,19,20 - tetranor - PGE_2 *p* - biphenylyl ester, 16 - phenoxy - 17,18,19,20 - tetranor - $PGF_{2\alpha}$ *p* - biphenylyl ester, and 16 - phenoxy 17,18,19,20 - tetranor - $PGF_{2\beta}$ *p*-biphenylyl ester.

Also preferred are the C_9 epimers of the compounds of Formula IA.

Especially preferred prostaglandins are the following:

A compound according to formula IIA wherein X is

$$\begin{matrix} O \\ \| \\ -CNHR'' \end{matrix}$$

R″ is acetyl, W is a *cis* double bond, Z is a *trans* double bond, R is hydrogen, n and m are each O, Ar is phenyl.

A compound according to formula IIA wherein X is 5-tetrazolyl, W is a *cis* double bond, Z is a *trans* double bond, R is hydrogen, n and m are each O, Ar is phenyl.

A compound according to formula IIA wherein X is

$$\begin{matrix} O \\ \| \\ -CNHR'' \end{matrix}$$

and R″ is methanesulfonyl, W is a *cis* double bond, Z is a *trans* double bond, R is hydrogen, n and m are each O, Ar is phenyl.

A compound according to formula IIA wherein X is

$$\begin{matrix} O \\ \| \\ -CNHR'' \end{matrix}$$

and R″ is methanesulfonyl, W is a *cis* double bond, Z is a *trans* double bond, R is hydrogen, n and m are each O, and Ar is *m*-methoxyphenyl.

The starting material for the various novel compounds of this invention are available commercially or are made by methods well known to those skilled in the art. For example, to make dimethyl 2-oxo-3-phenoxypropylphosphonate, the starting material for the synthesis of the 16-phenoxy-17,18,19,20-tetranor prostaglandins, one cools a solution of dimethyl methylphosphonate in tetrahydrofuran to −78°C in a dry nitrogen atmosphere and then adds *n*-butyllithium in hexane dropwise, slowly. After stirring, methyl 2-phenoxyacetate is added dropwise. After 3 to 4 hours at −78°C the reaction mixture is warmed to ambient temperature, neutralized with acetic acid and rotary evaporated to a white gel. The gelatinous material is taken up in water, the aqueous phase is extracted in chloroform and the combined organic extracts are backwashed, dried, and concentrated to give the desired product.

To make substituted 16-phenoxy-17,18,19,20-tetranor prostaglandins, one requires substituted phenoxyacetic acids which are prepared by condensation of appropriate phenol with a haloacetic acid or ester in presence of base as described by J. M. Petersen, Acta Chem. Scandinavica, *5*, 519 (1951) or M. Beroza, Agri. Food Chem., *4*, 49 (1956). Thus condensation of methyl bromoacetate with sesamol in the presence of sodium methoxide gives the *3,4-methylenedioxyphenoxyacetic acid methyl ester*. Similarly, one may prepare *p-chlorophenoxyacetic acid, 3,4,5-trimethoxyphenoxyacetic acid* and *p-phenylphenoxy acetic acid.*

These acids are converted to esters by the usual method and thence into phosphonates as described above for the unsubstituted 16-phenoxy starting compound.

To make the starting material for the 16-phenylpropoxy-17,18,19,20-tetranorprostaglandins, one requires the 2-(3-phenylpropoxy)acetic acid. This is prepared by method of Rothstein, Bull. Soc. Chim. *51*, 691, (1932), converted to the ester and thence to the phosphonate as described for the 16-phenoxy compound.

To prepare the 16-benzyloxy-17,18,19,20-tetranorprotaglandins, one requires 2-benzoyloxyacetic acid which is prepared by the method of H. Fisher and B. Gohlke, Helv. Chim. Acta, *16*, 1130 (1933) and converted to the ester by standard methods and thence to phosphonate by the method described for 16-phenoxy compound.

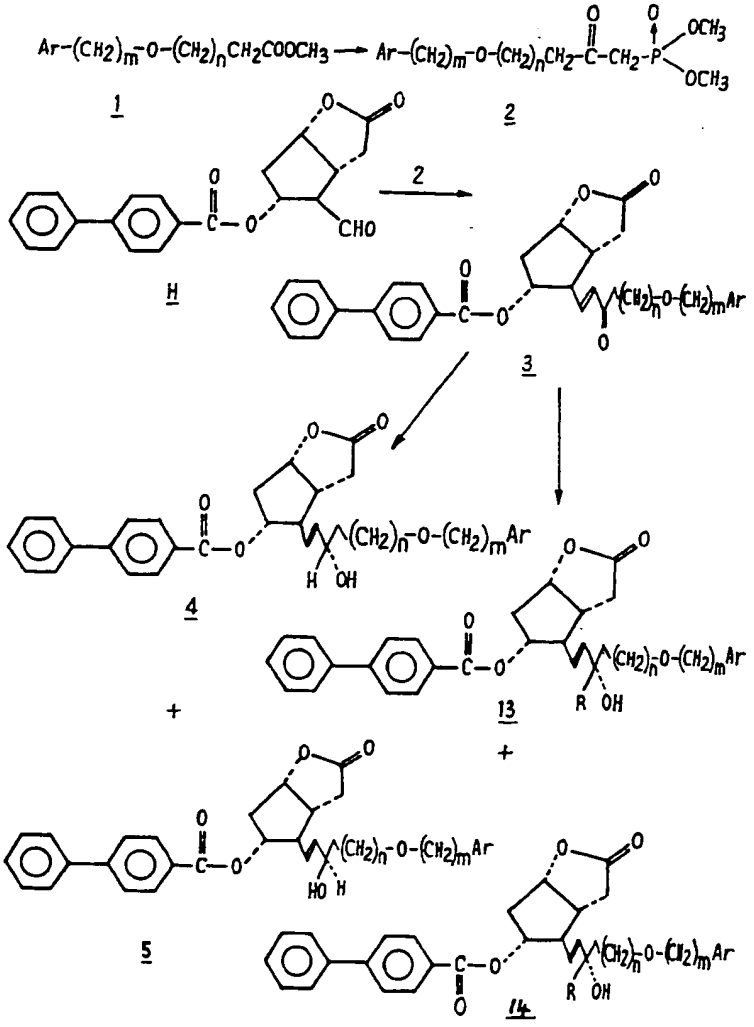
When 16-phenethoxy-17,18,19,20-tetranorprostaglandins are desired, one makes 2-(phenethoxy)acetic acid by, for example, the method of Rothstein, Bull. Soc. Chim., *51*, 691 (1932), converts it to the ester and thence to the phosphonate as described for the 16-phenoxy compound.

To prepare the 17-phenoxy-18,19,20-trisnor prostaglandins, 3-phenoxypropionic acid is converted to the ester and thence to the phosphonate as for the 16-phenoxy compound.

To prepare 18-phenoxy-19,20-bisnor prostaglandins, 4-phenoxybutyronitrile is refluxed with 10% aqueous methanolic HCl to convert it to the 4-phenoxybutyric acid suitable for conversion to phosphonate as described for the 16-phenoxy case.

To prepare the 19-phenoxy-20-nor prostaglandins, 5-phenoxyvaleric acid is prepared by the method of A. S. Carter, J. Am. Chem. Soc., *50*, 1967 (1928) and converted to the phosphonate as described for the 16-phenoxy case.

Scheme A



As shown in Scheme A, the first step in the complete synthesis (1→2) is the condensation of the appropriate ester with a dialkyl methylphosphonate to produce oxophosphonate *2*. These esters are obtained as previously described. The said oxophosphonates are described and claimed in Application No. 22858/76, (Serial No. 1,456,514).

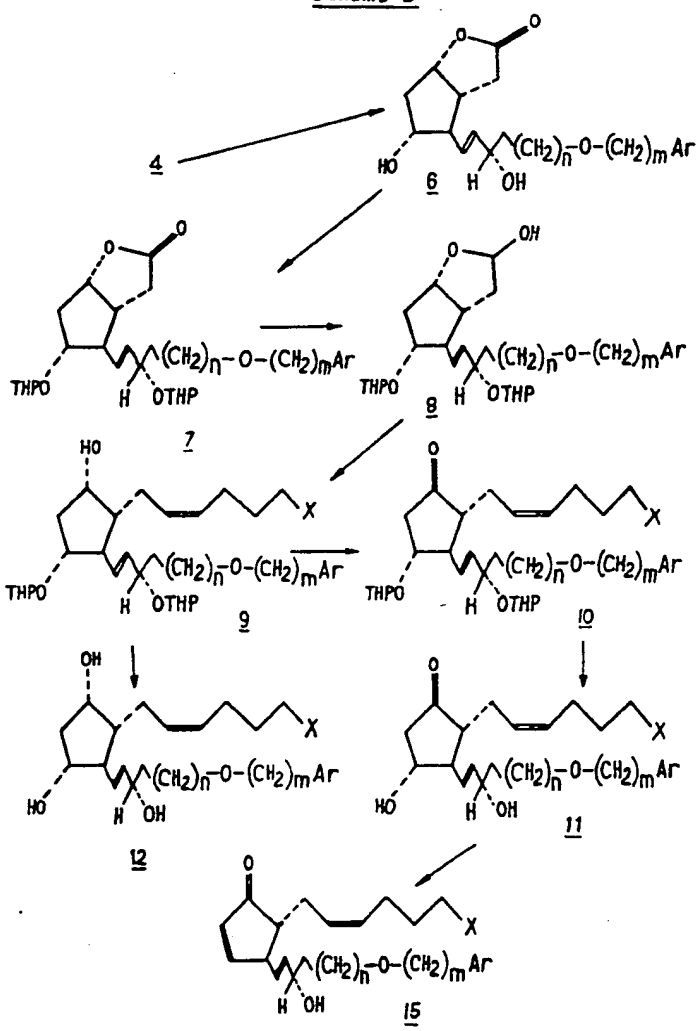
In *2→3* the oxophosphonate *2* is reacted with the known [Corey *et al.*, *J. Am.*

Chem. Soc., 93, 1491 (1971)] aldehyde H to produce, after chromatography or crystallization, the enone 3.

The enone *3* can be converted to a mixture of tertiary alcohols *13* and *14* by reaction with the appropriate metal alkyl and the isomeric *13* and *14* can be separated by column chromatography. The enone *3* can be reduced with zinc borohydride or with trialkylborohydrides, such as lithium triethylborohydride, to a mixture of alcohols, *4* and *5* which can be separated as above. In this reaction ethers such as tetrahydrofuran or 1,2-dimethoxyethane are usually employed as solvents, although occasionally methanol is preferred to ensure specificity of reduction. Further transformations of *4* are shown on Scheme B.:

4→*6* is a base catalyzed hydrolysis in which the *p*-biphenylyl-carbonyl protecting group is removed. This is most conveniently conducted with potassium carbonate in methanol or methanol-tetrahydrofuran solvent. *6*→*7* involves the protection of the two free hydroxyl groups with an acid-labile protecting group. Any sufficiently acid-labile group is satisfactory; however, the most usual one is 2-tetrahydropyranyl, which can be incorporated in the molecule by treatment with dihydropyran and an acid catalyst in an anhydrous medium. The catalyst is usually *p*-toluenesulfonic acid.

Scheme B



7→*8* is a reduction of the lactone *7* to the hemiacetal *8* using diisobutylaluminium hydride in an inert solvent. Low reaction temperatures are preferred and −60° to −70°C are usual. However, higher temperature may be employed if over-reduction does not occur. *8* is purified, if desired, by column chromatography. The compounds *3* to *8*; *13* and *14* are described and claimed in Application No. 23950/76, (Serial No. 1,456,513).

8→*9* is a Wittig condensation in which hemiacetal *8* is reacted with (4-carboxybutyl)triphenylphosphonium bromide in dimethyl sulfoxide, in the presence of sodium methylsulfinylmethide. *9* is purified as above.

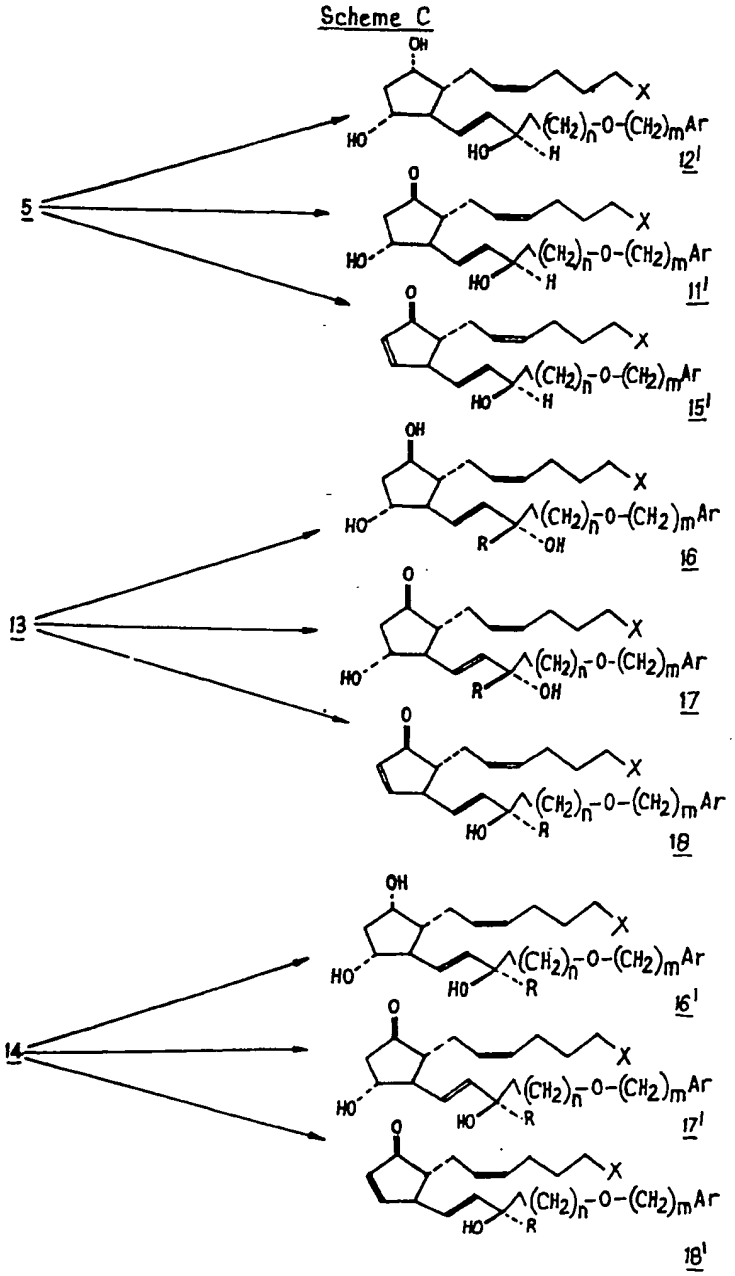
The conversion *9*→*12* is an acidic hydrolysis of the tetrahydropyranyl groups. Any acid may be used which does not cause destruction of the molecule in the course of the removal of the protecting group; however, this is accomplished most often by use of 65% v/v aqueous acetic acid. The product is purified as above.

9→*10* is an oxidation of the secondary alcohol *9* to the ketone *10*. This may be accomplished using any oxidizing agent which does not attack double bonds; however, the Jones reagent is usually preferred. The product is purified as above.

10→*11* is carried out in the same manner as *9*→*12*. The product is purified as above.

11→*15* is an acid-catalyzed dehydration. Any acid may be used for the process which does not cause extensive decomposition of the product, but the most usual procedure consists of dissolving *11* in an excess of 97% formic acid followed by dilution with ice water and extraction of the product after the starting material has been consumed. The product is purified as above.

Scheme C



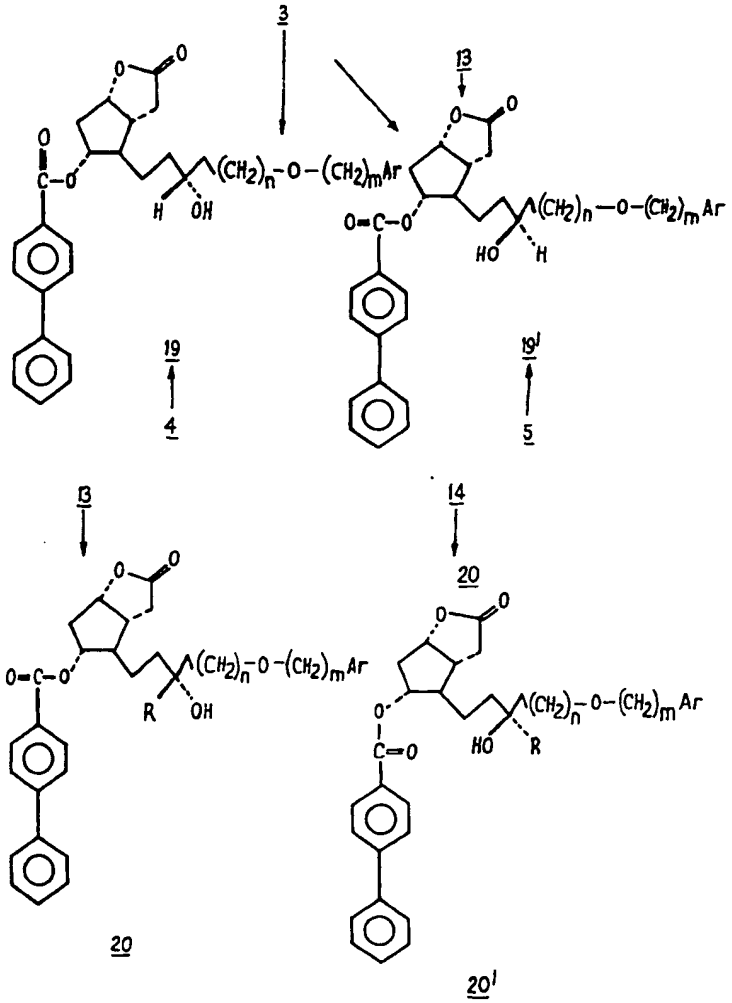
As is illustrated in scheme C, *5*, *13* and *14* may be substituted for *4* in scheme B to provide prostaglandin derivatives *12'*—*18'*.

Scheme D illustrates the synthesis of precursors to the 13,14-dihydro-15-substituted-16,17,18,19,20-pentanorprostaglandins.

In *3*→*19* + *19'* the enone *3* is reduced to the tetrahydro compound through the use of any of the complex metal hydride reducing agents, $LiAlH_4$, $NaBH_4$, KBH_4, $LiBH_4$ and $Zn(BH_4)_2$. Especially preferred is $NaBH_4$. The products, *19* and *19'*, are separated from each other by column chromatography.

Furthermore, the compounds *4* and *5* of Scheme A can be reduced catalytically with hydrogen to *19* and *19'* respectively. The stage at which the double bond is reduced is not critical, and hydrogenation of *6* or *7* of scheme B will also afford useful intermediates for the 13,14-dihydro-prostaglandin analogs of the present invention. This reduction may be achieved with either a homogenous catalyst such as tris(triphenylphosphine)chlororhodium, or with a heterogeneous catalyst such as platinum, palladium or rhodium. In a similar way the precursors to the 15-lower alkyl-15-substituted-16,17,18,19,20-pentanorprostaglandins are synthesized by substituted compounds *13* and *14* for *4* and *5* respectively, in the synthesis just described. The conversion of *19*, *19'*, *20'* and *20* to their respective prostaglandins follows the route shown in scheme B when *4* is replaced by *19*, *19'*, *20'* and *20* to yield the 13,14-dihydro-PGE_2,-PGA_2 and -PGF_2 series of prostaglandin derivatives containing hydrogen or lower alkyl group at carbon 15.

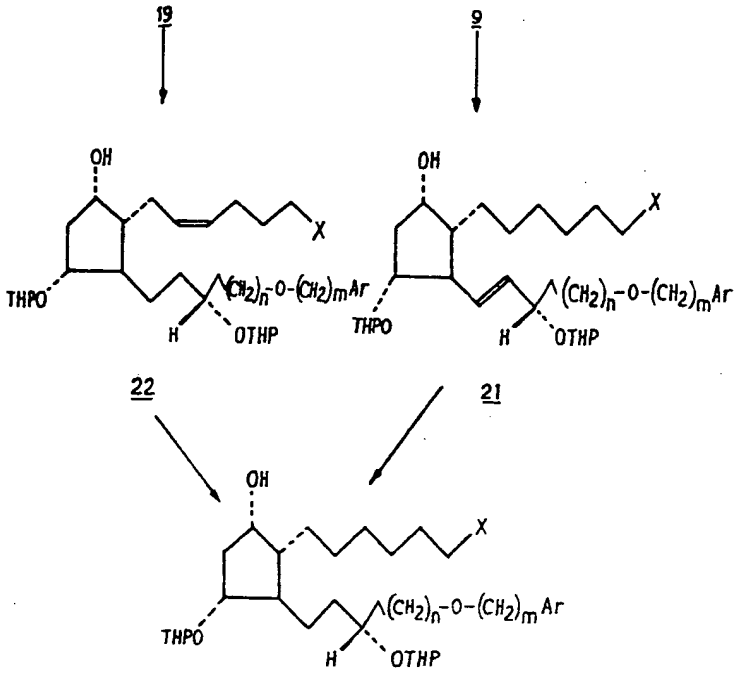
Scheme D



Scheme E illustrates the preparation of the various reduced 15-substituted-16,17,18,19,20-pentanorprostaglandin precurosrs:

19→22 is carried out as illustrated on Scheme B for *4→9*. *22* can be used as both a precursor to a 13,14-dihydro-15-substituted-16,17,18,19,20-pentanorprostaglandin of the "2-series" or as an intermediate to *23*, a precursor to a 13,14-dihydro-15-substituted-16,17,18,19,20-pentanorprostaglandin of the "1-series". *22→23* is carried out by catalytic hydrogenation using the catalyst described for the reduction of *4→19* of Scheme D. Intermediates of the type *21* are prepared by selective reduction of the 5,6-*cis* double bond at low temperature using catalysts such as those described for *4→19* and *17→23*. Especially preferred for this reduction is the use of palladium on carbon as a catalyst and a reaction temperature of -20°C. Intermediates of the type *21* are not only precursors to 15-substituted-16,17,18,19,20-pentanorprostaglandins of the "1-series" through the route *9→15* of scheme B, but also as a precursor to compounds of the type *23* through the route already discussed for *22→23*.

Scheme E



Furthermore, the 15-substituted-16,17,18,19,20-pentanorprostaglandins of the E_1 and $F_{1\alpha}$ series may be obtained directly from the corresponding prostaglandin analog of the "2-series" by first protecting the hydroxyl by introducing dimethylisopropylsilyl groups, reducing selectively the *cis* double bond, and removing the protecting group.

The introduction of the protecting group is usually accomplished by treatment of the prostaglandin analog with dimethylisopropylchlorosilane and triethylamine, the reduction is accomplished as discussed above for *9→21* and removal of the protecting group is accomplished by contacting the reduced protected compound with 3:1 v/v acetic acid: water for 10 minutes or until reaction is substantially complete.

The C_{15} epimers of *21*, *22* and *23* can be used as precursors to the 15-*epi* series of prostaglandin derivatives described above, and 15-(loweralkyl)-15-substituted-16,17,18,19,20-pentanorprostaglandin reduced at the 5,6- and/or the 13,14-position and their C_{15} epimers can be prepared from the appropriately substituted analogs of *9* and *19* whose syntheses follow those of Scheme A and B.

13,14-dihydro-15-(lower alkyl)-15-substituted-16,17,18,19,20-pentanorprostaglandins are available from the appropriately substituted precursors *via* Scheme E.

In the foregoing procedures, where purification by chromatography is desired, appropriate chromatographic supports include neutral alumina and silica

gel and 60—200 mesh silica gel is generally preferred. The chromatography is suitably conducted in reaction-inert solvents such as ether, ethyl acetate, benzene, chloroform, methylene chloride, cyclohexane and n-hexane, as further illustrated in the appended examples.

It will be seen that the foregoing formulae depict optically active compounds. It will be clear, however, that the corresponding racemates will exhibit valuable biological activity by virtue of their content of the above-mentioned biologically active optical isomer, and it is intended that such racemates also be embraced by the foregoing formulae herein and in the appended claims. The racemic mixtures are readily prepared by the same methods employed herein to synthesize the optically active species, by mere substitution of corresponding racemic precursors in place of optically active starting materials.

In numerous *in vivo* and *in vitro* tests we have demonstrated that the new prostaglandin analogs possess physiological activities comparable to those exhibited by the natural prostaglandins. These tests include, among others, a test for effect on isolated smooth muscle from guinea pig uterus, guinea pig ileum and rat uterus, inhibition of histamine-induced bronchospasm in the guinea pig, and effect on dog blood pressure, inhibition of stress-induced ulceration in the rat, inhibition of gastric acid and pepsin secretion in rat and dog, inhibition of collagen or ADP-induced blood platelet aggregation and abortifacient activity in rats and guinea pigs by luteolytic and non-luteolytic mechanisms.

The physiological responses observed in these tests are useful in determining the utility of the test substance for the treatment of various natural and pathological conditions. Such determined utilities include: antihypertensive activity, bronchodilator activity, antithrombogenic activity, antiulcer activity, smooth muscle activity [useful as an anti-fertility agent, for the induction of labor, and as an abortifacient], and anti-fertility activity through a mechanism not affecting smooth muscle, for example, luteolytic mechanisms, and the synchronization of the estrous cycle in farm animals.

The novel compounds of this invention possess more selective activity profiles than the corresponding naturally occurring prostaglandins, and in many cases, exhibit a longer duration of action. The 15-substituted-16,17,18,19,20-pentanor-prostaglandins of the PGE_0, $F_{0\beta}$, $F_{1\beta}$, $F_{2\beta}$, and 13,14-dihydro-$PGF_{2\beta}$ of the invention exhibit smooth muscle stimulant activity, whereas the corresponding derivatives of the A_0, A_1, A_2 and 13,14-dihydro-PGA_2 series have gastric antisecretory/antiulcer activity.

Particularly useful for fertility control, abortion and induction of labor are the 16-phenoxy-17,18,19,20-tetranorprostaglandins of the invention of the E_2, $F_{2\alpha}$ and $F_{2\beta}$ series based on especially outstanding smooth muscle stimulating activity, and at the same time reduced blood pressure effects. Similarly, the substituted 16,17,18,19,20-pentanorprostaglandins of the invention of the PGE_1, $PGF_{0\alpha}$, $PGF_{1\alpha}$, and 13,14-dihydro-$PGF_{2\alpha}$ series are useful for fertility control including abortion and induction of labor on the basis of their smooth muscle stimulant activity. The novel 15-substituted-16,17,18,19,20-pentanorprostaglandin-13,14-dihydro-E_2 analogs can be employed in the treatment of peptic ulcers. The novel prostaglandins with a β-OH at the 15-position are in general less potent, although frequently more selective than the corresponding α-hydroxyl epimers. Additionally, the prostaglandins having a β-hydroxyl at C-15 are valuable intermediates to prostaglandins having a α-hydroxyl at C-15 through a recycling process involving an oxidation and reduction at C-15.

The novel 15 lower alkyl compounds of this invention have the same profile of activity as the prostaglandin analogs of this invention, where R is hydrogen, from which they are derived. Their special utility is concerned with the fact that their duration of action is much increased over the above said compounds, where R is hydrogen, and in such cases where this is essential the 15-lower alkyl compounds are usually preferred. The prostaglandin analogs which have a beta hydroxyl at C_{15} and possess a C_{15} lower alkyl group have action which is similar to their epimers. In some cases, however, the selectivity that these compounds display exceeds that of the epimeric compounds.

The new compounds of this invention can be used in a variety of pharmaceutical formulations which contain the compound, and they may be administered in the same manner as natural prostaglandins by a variety of routes, such as intravenous, oral, intravaginal, intra- and extra-amniotic, among others.

For induction of abortion, tablets or an aqueous suspension or alcoholic solution of a 16-phenoxy-17,18,19,20-tetranorprostaglandin of the invention would

appropriately be administered at oral doses of 0.1—20 mg., with 1—7 doses per day being employed. For intravaginal administration a suitable formulation would be lactose tablets or an impregnated tampon of the same agent. For such treatments suitable doses would be from 0.1—20 mg/dose with 1—7 doses being employed. For intra-amniotic administration a suitable formulation would be an aqueous solution containing 0.05—10 mg/dose with 1—7 doses being employed. For extra-amniotic administration a suitable formulation would be an aqueous solution containing 0.005—1 mg/dose with 1—5 doses being employed. Alternatively, the 16-phenoxy-17,18,19,20-tetranorprostaglandins of this invention can be infused intravenously for induction of abortion at doses of 0.05—50 μg/minute for a period of from 1—24 hours. For synchronization of the estrous cycle in pigs, sheep, cows or horses, a solution or suspension containing 0.03—30 mg/day of a 16-phenoxy-17,18,19,20-tetranorprostaglandin of the invention is administered subcutaneously from 1—4 days.

15-substituted-16,17,18,19,20-pentanorprostaglandins of the invention of the A series are useful gastric antisecretory and antiulcer agents, as are the 15-substituted-16,17,18,19,20-pentanorprostaglandins of the invention of the E series. For treatment of peptic ulcers these compounds are administered preferably orally in the form of capsules or tablets at doses of 0.001 to 0.1 mg/kg/day.

To prepare any of the above dosage forms or any of the numerous other forms possible, various reaction-inert diluents, excipients or carriers may be employed. Such substances include, for example, water, ethanol, gelatins, lactose, starches, magnesium stearate, talc, vegetable oils, benzyl alcohols, gums, polyalkylene glycols, petroleum jelly, cholesterol, and other known carriers for medicaments. If desired, these pharmaceutical compositions may contain auxiliary substances such as preserving agents, wetting agents, stabilizing agents, or other therapeutic agents such as antibiotics.

Various modifications are possible on the upper side chain of the prostaglandins of this invention; such modifications do not, as a rule, alter the basic biological activity of the prostaglandin, although they may increase selectivity and duration of action further and reduce toxicity. For example, a 5-tetrazoyl group may be placed at the C_1 position as described in United Kingdom Patent Specification No. 1373461. For example, 2-decarboxy-2-(tetrazol-5-yl)-16-phenoxy-PGE_2 has the same utility as 16-phenoxy-PGE_2 biphenylyl ester; namely, for induction of labor or abortion, and for the inhibition of gastric acid secretion and treatment of peptic ulcers.

Another upper side chain modification which may be made in the prostaglandins of this invention is substitution of the carboxylate group at the C_1 position by a carboxamide group. The methods for preparing these compounds are disclosed in United Kingdom Patent Specification No. 1,439,511. Alternatively, the novel compounds of this invention represented by formulae I and II (where X is

$$\overset{O}{\overset{\|}{C}}NHR''$$

and wherein R'' is as defined previously), may be prepared from compound 10 of Scheme B (or the corresponding 15-epimers of 15-lower alkyl derivatives of 10) by reaction with appropriate isocyanates, followed by hydrolysis with dilute acid. The utility of *N*-methylsulfonyl-16-phenoxy-17,18,19,20-tetranor-PGE_2-carboxamide, for example, is the same as that of 16-phenoxy PGE_2 diphenylyl ester.

The *p*-biphenylyl esters of the invention are prepared in the Examples by simply adding *p*-phenylphenol to the prostaglandin preferably in methylene chloride in the presence of a dehydrating agent for example, *N,N'*-dicyclohexykcarbodiimide, and stirring overnight. Although not more potent in *in vitro* smooth muscle tests, abortifacient evaluation of 16-phenoxy-17,18,19,20-tetranor-PGE_2 and -$PGF_{2\alpha}$ *p*-biphenylyl esters demonstrated that these *p*-biphenylyl-esters possess physiological activities markedly greater than those of the free acids.

The following non-limiting Examples XXI, XXIII, XXIV to XXXI and XXXIII to XXXVIII illustrate the invention. In these Examples it will be appreciated that all temperatures are expressed in Centigrade, all melting and boiling points are uncorrected.

The words "Mallinckrodt" and "Darco" are registered Trade Marks.

EXAMPLE I.

Dimethyl 2-Oxo-3-phenoxypropylphosphonate:

A solution of 33.2 g (268 mmoles) dimethyl methylphosphonate (Aldrich) in 360 ml dry tetrahydrofuran was cooled to −78° in a dry nitrogen atmosphere. To the stirred phosphonate solution was added 118 ml of 2.34 *M* *n*-butyllithium in hexane solution (Alfa Inorganics, Inc.) dropwise over a period of 18 minutes at such a rate that the reaction temperature never rose above −65°. After an additional 5 minutes stirring at −78°, 22.2 g (134 mmole) methyl 2-phenoxy acetate was added dropwise at a rate that kept the reaction temperature less than −70° (20 minutes). After 3.5 hours at −78° the reaction mixture was allowed to warm to ambient temperature, neutralized with 14 ml acetic acid and rotary evaporated to a white gel. The gelatinous material was taken up in 175 ml water, the aqueous phase extracted with 100 ml portions of chloroform (3x), the combined organic extracts were backwashed (50 cc H_2O), dried ($MgSO_4$), and concentrated (water aspirator) to a crude residue and distilled, b.p. 172—175° (0.5 mm) to give 24.6 g dimethyl 2-oxo-3-phenoxypropylphosphonate.

The nmr spectrum ($CDCl_3$) showed a doublet centered at 3.75δ (J=11.5 cps, 6H) for

$$(CH_3O)—\overset{\overset{O}{\|}}{P}—$$

a singlet at 4.7δ (2H) for $C_6H_5O—CH_2—CO—$, a doublet centered at 3.24δ (J=23 cps, 2H)

$$—\overset{\overset{O}{\|}}{C}—CH_2—P—$$

and a multiplet at 6.8—7.5δ (5H) for the aromatic protons.

EXAMPLE II.

2-[3α-*p*-Phenylbenzoyloxy-5α-hydroxy-2β-(3-oxo-4-phenoxy-*trans*-1-butenyl)cyclopent-1α-yl]Acetic Acid, γ-lactone:

Dimethyl 2 - oxo - 3 - phenoxypropylphosphonate (5.4 g), 21 mmole) in 200 ml anhydrous diethyl ether was treated with 7.9 ml (19 mmole) 2.5 *M* *n*-butyllithium in *n*-hexane (Alfa Inorganics, Inc.) in a dry nitrogen atmosphere at room temperature. After 5 min. of stirring, an additional 400 ml. of anhydrous ether was added followed by 6.0 g (17 mmole) 2 - [3α - *p* - phenylbenzoyloxy - 5α - hydroxy - 2β - formylcyclopent - 1α - yl]acetic acid, γ-lactone in one portion and 50 ml anhydrous diethyl ether. After 35 minutes the reaction mixture was quenched with 5 ml glacial acetic acid and washed with 100 ml saturated sodium bicarbonate solution (4 x), 100 ml water (2 x), 100 ml saturated brine (1 x), dried ($MgSO_4$) and evaporated to yield 5.2 gm 2 - [3α - *p* - phenylbenzoyloxy - 5α - hydroxy - 2β - (3 - oxo - 4 - phenoxy - *trans* - butenyl)cyclopent - 1α - yl]acetic acid, γ-lactone as a solid after column chromatography (Silica gel, Baker, 60—200 mesh); m.p. 112—114° after crystallization from methylene chloridehexane.

The ir spectrum (KBr) of the product exhibited absorption bands at 1775 cm^{-1} (strong), 1715 cm^{-1} (strong), 1675 cm^{-1} (medium) and 1630 cm^{-1} (medium) attributable to the carbonyl groups and at 970 cm^{-1} for the *trans* double bond.

EXAMPLE III.

2 - [3α - *p* - Phenylbenzoyloxy - 5α - hydroxy - 2β - (3α - hydroxy - 4 - phenoxy - *trans* - 1 - butenyl)cyclopent - 1α - yl]acetic acid, γ - lactone:

To a solution of 5.1 g (10.5 mmole) 2 - [3α - *p* - phenylbenzoyloxy - 5α - hydroxy - 2β - (3 - oxo - 4 - phenoxy - *trans* - 1 - butenyl)cyclopent - 1α - yl]acetic acid, γ - lactone in 30 ml dry 1,2 - dimethoxyethane in a dry nitrogen atmosphere at ambient temperature was added dropwise 11 ml (5.5 mmole) of a 0.5 *M* zinc borohydride solution. After stirring at room temperature for 2 hours, a saturated sodium bitartrate solution was added dropwise until hydrogen evolution ceased. The reaction mixture was allowed to stir for 5 minutes at which time 250 ml dry methylene chloride was added. After drying ($MgSO_4$) and concentrating (water aspirator) the resultant semisolid was purified by column chromatography on silica gel (Baker "Analyzed" Reagent 60—200 mesh) using ether as eluent. After

elution of less polar impurities a fraction containing 896 mg 2 - [3α - *p* - phenylbenzoyloxy - 5α - hydroxy - 2β - (3α - hydroxy - 4 - phenoxy - *trans* - 1 - butenyl)-cyclopent - 1α - yl]acetic acid, γ - lactone, a 600 mg fraction of mixed *4* and *5* and finally a fraction (1.5 gm) of 2 - [3α - *p* - phenylbenzoyloxy - 5α - hydroxy - 2β - (3β - hydroxy - 4 - phenoxy - *trans* - 1 - butenyl)cyclopent - 1α - yl]acetic acid, γ - lactone.

The ir spectrum ($CHCl_3$) of *4* had strong carbonyl absorptions at 1770 and 1715 cm^{-1} and an absorption at 970 cm^{-1} for the *trans* double bond.

EXAMPLE IV.

2 - [3α,5α - Dihydroxy - 2β - (3α - hydroxy - 4 - phenoxy - *trans* - 1 - butenyl) cyclopent - 1α - yl]acetic acid, γ - lactone:

A heterogeneous mixture of 846 mg (1.7 mmole) of 2 - [3α - *p* - phenyl - benzoyloxy - 5α - hydroxy - 2β - (3α - hydroxy - 4 - phenoxy - *trans* - 1 - butenyl)-cyclopent - 1α - yl]acetic acid, γ - lactone, 10 ml of absolute methanol and 120 mg of finely powdered, anhydrous potassium carbonate was stirred at room temperature for 20 hours, then cooled to 0°. To the cooled solution was added 1.75 ml of 1.0*N* aqueous hydrochloric acid. After stirring at 0° for an additional 10 minutes, 10 ml. of water was added with concomitant formation of methyl *p*-phenylbenzoate which was collected by filtration. The filtrate was saturated with solid sodium chloride, extracted with ethyl acetate (4 x 10 ml.), the combined organic extracts were washed with saturated sodium bicarbonate (10 ml.) dried ($MgSO_4$) and concentrated to give 445 mg of viscous, oily 2 - [3α,5α - dihydroxy - 2β - (3α - hydroxy - 4 - phenoxy - *trans* - 1 - butenyl)cyclopent - 1α - yl]acetic acid, γ - lactone.

The ir spectrum ($CHCl_3$) exhibited a strong absorption at 1772 cm^{-1} for the lactone carbonyl and medium absorption at 965 cm^{-1} for the *trans*-double bond.

EXAMPLE V.

2 - [5α - Hydroxy - 3α - (tetrahydropyran - 2 - yloxy) - 2β - (3α - tetrahydropyran - 2' - yloxy - 4 - phenoxy - *trans* - 1 - butenyl)cyclopent - 1α - yl]acetic acid, γ - lactone:

To a solution of 445 mg (1.46 mmole) 2 - [3α,5α - dihydroxy - 2β - (3α - hydroxy - 4 - phenoxy - *trans* - 1 - buten - yl)cyclopent - 1α - yl]acetic acid, γ - lactone in 5 ml anhydrous methylene chloride and 0.4 ml of 2,3 - dihydropyran at 0° in a dry nitrogen atmosphere was added 5 mg *p*-toluenesulfonic acid, monohydrate. After stirring for 15 minutes, the reaction mixture was combined with 100 ml ether, the ether solution washed with saturated sodium bicarbonate (1 x 15 ml) then saturated brine (1 x 15 ml), dried ($MgSO_4$) and concentrated to yield 752 mg (>100%) crude 2 - [5α - hydroxy - 3α - (tetrahydropyran - 2 - yloxy) - 2β - (3α - tetrahydropyran - 2' - yloxy - 4 - phenoxy - *trans* - 1 - butenyl)cyclopent - 1α - yl]-acetic acid, γ-lactone.

The ir ($CHCl_3$) spectrum had a medium absorption at 970 cm^{-1} for the *trans*-double bond, and at 1770 cm^{-1} for lactone carbonyl.

EXAMPLE VI.

2[5α - Hydroxy - 3α - (tetrahydropyran - 2 - yloxy) - 2β - (3α - tetrahydropyran - 2' - yloxy - 4 - phenoxy - *trans* - 1 - butenyl)cyclopent - 1α - yl]acetaldehyde, γ - hemiacetal:

A solution of 690 mg (1.46 mmole) 2 - [5α - hydroxy - 3α - (tetrahydropyran - 2 - yloxy) - 2β - (3α - tetrahydropyran - 2' - yloxy - 4 - phenoxy - *trans* - 1 - butenyl) cyclopent - 1α - yl]acetic acid, γ - lactone in 8 ml dry toluene was cooled to –78° in a dry nitrogen atmosphere. To this cooled solution was added 2.0 ml of 20% diisobutylaluminium hydride in n-hexane (Alfa Inorganics) dropwise at such a rate so that the internal temperature never rose above –65° (15 minutes). After an additional 45 minutes of stirring at –78°, anhydrous methanol was added until gas evolution ceased and the reaction mixture was allowed to warm to room temperature. The reaction mixture was combined with 100 ml ether, washed with 50% sodium potassium tartrate solution (4 x 20 ml), dried (Na_2SO_4) and concentrated to yield 613 mg 2 - [5α - hydroxy - 3α - (tetrahydropyran - 2 - yloxy) - 2β - (3α - tetrahydropyran - 2 - yloxy - 4 - phenoxy - trans - 1 - butenyl)cyclopent - 1 - yl]acetaldehyde, γ - hemiacetal.

EXAMPLE VII.

9α - Hydroxy - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoic acid:

To a solution of 1.6 gm (3.6 mmole) (4 - carboxybutyl)triphenylphosphonium bromide in a dry nitrogen atmosphere in 6.0 ml dry dimethyl sulfoxide was added 3.24 ml (6.5 mmole) of a 2.0*M* solution of sodium methylsulfinylmethide in dimethyl sulfoxide. To this red ylide solution was added dropwise a solution of 613 mg (1.29 mmole) 2 - [5α - hydroxy - 3α - (tetrahydropyran - 2 - yloxy) - 2β - (3α - tetrahydropyran - 2' - yloxy - 4 - phenoxy - *trans* - 1 - butenyl)cyclopent - 1α -yl]-acetaldehyde, γ - hemiacetal in 5.0 ml dry dimethyl sulfoxide over a period of 20 minutes. After an additional 2 hours stirring at room temperature, the reaction mixture was poured onto ice water. The basic aqueous solution was washed twice with ethyl acetate (20 ml) and acidified to pH 3 with 10% aqueous hydrochloric acid. the acidic solution was extracted with ethyl acetate (3 × 20 ml) and the combined organic extracts washed once with water (10 ml), dried ($MgSO_4$) and evaporated to a solid residue. This solid residue was triturated with ethyl acetate and the filtrate concentrated to yield 754 mg of 9α - hydroxy - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoic acid was collected. Infra-red spectrum ($CHCl_3$) displayed a strong band at 1720 cm^{-1} for the carboxyl group.

EXAMPLE VIII.

9 - Oxo - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoic acid:

To a solution cooled to −10° under nitrogen of 754 mg (1.3 mmole) 9α-hydroxy - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoic acid in 13 ml reagent grade acetone was added dropwise to 0.56 ml (1.41 mmole) of Jones' reagent. After 20 minutes at −10°, 0.260 ml. 2-propanol was added and the reaction mixture was allowed to stir an additional 5 minutes at which time it was combined with 75 ml ethyl acetate, washed with water (3 × 10 ml.), dried ($MgSO_4$) and concentrated to give 752 mg. of 9 - oxo - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoic acid, which was chromatographed on silica gel using ethyl acetate as eluent to afford 505 mg. of pure *10*.

EXAMPLE IX.

9 - Oxo - 11α,15α - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoic acid:

A solution of 505 mg (0.9 mmole) 9 - oxo - 11α,15α - *bis* - (tetrahydropyran-2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoic acid in 6.3 ml. of a 65:35 mixture of glacial acetic acid:water was stirred under nitrogen at 25° for 18 hours then was concentrated by rotary evaporation. The resultant crude oil was purified by column chromatography on silica gel ("Mallinckrodt" CC-4 100—200 mesh) using ethyl acetate as eluent. After elution of less polar impurities the oily 9 - oxo - 11α,15α - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoic acid weighing 210 mg. was collected.

Ir ($CHCl_3$) displayed a broad band at 1725 cm^{-1} for carbonyl absorptions, and a band at 970 cm^{-1} for the 13,14 - *trans* - double bond.

EXAMPLE X.

9α,11α,15α - trihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoic acid:

A mixture of 375 mg (0.65 mmole) 9α - hydroxy - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoic acid, acetic acid (6.5 ml) and water (3.5 ml) was stirred under nitrogen at room temperature for 20 hours. The resulting clear solution was concentrated under reduced pressure and the residue (380 mg) was dissolved in ethyl acetate. The ethyl acetate solution was washed with brine (20 ml), dried ($NaSO_4$) and concentrated to a clear oil. Chromatography on silica gel (Mallinckrodt CC-7) using chloroform and then ethyl acetate as eluent afforded the desired product, 9α,11α,15α - trihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoic acid as a colorless oil weighing 98 mg.

EXAMPLE XI.

9α - Hydroxy - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranorprostanoic acid:

A mixture of 190 mg (0.33 mmole) 9α - hydroxy - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoic acid, 5% palladium on carbon (150 mg) in methanol (10 ml) is stirred under an atmosphere of hydrogen for 60 hours at room temperature. The mixture is filtered and concentrated to give 9α - hydroxy - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - tetranorprostanoic acid.

EXAMPLE XII.

9α,11α,15α - Trihydroxy - 16 - phenoxy - 17,18,19,20 - tetranorprostanoic acid:

Hydrolysis of 20 mg 9α - hydroxy - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - prostanoic acid is carried out with acetic acid (0.5 ml) and water (0.3 ml) under nitrogen at room temperature for 20 hours. Purification as described in Example X affords pure 9α,11α,15α - trihydroxy - 16 - phenoxy - 17,18,19,20 - tetranorprostanoic acid.

EXAMPLE XIII.

9 - Oxo - 11α,15α - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranorprostanoic acid:

A solution of 186 mg (0.3 mmole) of the product of Example XI in 3 ml acetone is oxidized with 0.14 ml (0.35 mmole) of Jones' reagent as described in Example VIII. Isolation of the product and hydrolysis with acetic acid and water at room temperature as described in Example IX gives pure 9 - oxo - 11α,15α - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranorprostanoic acid.

EXAMPLE XIV.

9 - Oxo - 15α - hydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5,10, *trans* - 13 - prostatrienoic acid:

A mixture of 52 mg (0.1 mmole) 9 - oxo - 11α,15α - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoic acid with 0.2 ml 97% formic acid is stirred at 25° for 2.5 hours. About 5 ml ice-water is added to the reaction mixture which is then extracted with ethyl acetate, dried (Na_2SO_4) and concentrated to give a crude oil. Chromatography of the crude product on silica gel (Mallinckrodt CC-7) using methylene chloride-ethyl acetate as eluent gives the desired 9 - oxo - 15α - hydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5,10,*trans* - 13 - prostatrienoic acid.

EXAMPLE XV.

9 - Oxo - 15α - hydroxy - 16 - phenoxy - 17,18,19,20 - tetranorprost - 10 - enoic acid:

9 - oxo - 11α,15α - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranorprostanoic acid is treated with 97% formic acid as described in Example XIV and converted to colorless oil 9 - oxo - 15α - hydroxy - 16 - phenoxy - 17,18,19,20 - tetranorprost - 10 - enoic acid.

EXAMPLE XVI.

2 - [3α - *p* - Phenylbenzoyloxy - 5α - hydroxy - 2β - (3 - hydroxy - 3 - methyl - 4 - phenoxy - *trans* - 1 - butenyl)cyclopent - 1α - yl]acetic acid, γ - lactone

To a solution of 2 - [3α - *p* - phenylbenzoyloxy - 5α - hydroxy - 2β - (3 - oxo - 4 - phenoxy - *trans* - 1 - butenyl)cyclopent - 1α - yl]acetic acid, γ - lactone cooled to −78° in diethyl ether-THF, is added dropwise one equivalent of 2N solution of methyl lithium in ether. After stirring at −78° for 15 minutes the reaction is quenched by addition of glacial acetic acid, sufficient to bring pH up to 7. The mixture is diluted with methylene chloride, washed with water, saturated brine, dried (Na_2SO_4) and concentrated to give the oily epimeric alcohols. The crude product is purified by column chromatography on silica gel to give the desired 2 - [3α - *p* - phenylbenzyloxy - 5α - hydroxy - 2β - (3 - hydroxy - 3 - methyl - 4 - phenoxy - *trans* - 1 - butenyl)cyclopent - 1α - yl]acetic acid, γ-lactone, which may be converted to give *17* and *17'* through steps previously outlined for the preparation of 9 - oxo - 11α,15α - dihydroxy - 16 - phenoxy - 17,18,19,20 - *cis* - 5 - *trans* - 13 - prostadienoic acid.

EXAMPLE XVII.

2 - [3α - *p* - Phenylbenzyloxy - 5α - hydroxy - 2β - (3α - hydroxy - 4 - phenoxy - butyl) cyclopent - 1α - yl]acetic acid, *p*-lactone:

A heterogenous solution of 2.5 g of 2 - [3α - *p* - phenylbenzoyloxy - 5α - hydroxy - 2β - (3α - hydroxy - 4 - phenoxy - *trans* - 1 - butenyl)cyclopent - 1α - yl]-acetic acid, *p*-lactone and 0.25 g of 5% palladium on charcoal in 30 ml of absolute methanol is stirred under 1 atmosphere of hydrogen for 4 hours. The mixture is then filtered and concentrated to afford 2 - [3α - *p* - phenylbenzoyloxy - 5α - hydroxy - 2β - (3 - oxo - 4 - phenoxybutyl)cyclopent - 1α - yl]acetic acid, *p* - lactone.

To a solution of 1.9 g of the crude hydrogenation product above in 20 ml of absolute methanol is added excess sodium borohydride and the solution is stirred at room temperature under nitrogen for 2 hours, and then concentrated. The residue is diluted with 0.1 *N* hydrochloric acid and the aqueous layer is extracted with ethyl acetate. The combined organic extracts are washed with saturated brine, are dried (Na_2SO_4), and are concentrated. Purification of the crude residue by silica gel chromatography affords 2 - [3α - *p* - phenylbenzyloxy - 5α - hydroxy - 2β - (3α - hydroxy - 4 - phenoxybutyl)cyclopent - 1α - yl]acetic acid, *p* - lactone and the 3β - hydroxy epimer.

This is converted to the 13,14 - dihydro E_2 and $F_{2\alpha}$ compounds using methods employed in Examples V to IX.

EXAMPLE XVIII.

9α - Hydroxy - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *trans* - 13 - prostenoic acid:

A heterogeneous mixture of 800 mg of 9α - hydroxy - 11α,15α - *bis* - (tetra - hydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - trans - 13 - prostadienoic acid and 80 mg of 5% palladium on charcoal in 10 ml of absolute methanol is stirred under 1 atmosphere of hydrogen at −22° for 5 hours. The mixture is then filtered and the filtrate is concentrated to afford 9α - hydroxy - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - 13 - *trans* - prostenoic acid.

Hydrolysis with acetic acid and water in the usual manner affords 16 - phenoxy - $PGF_{1\alpha}$.

EXAMPLE XIX.

9 - oxo - 11α,15α - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *trans* - 13 - prostenoic acid:

A solution of 72 mg 9 - oxo - 11α,15α - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoic acid in 5 ml of anhydrous diethyl ether is treated with 450 mg dimethylisopropylchlorosilane and 36 mg of triethylamine at room temperature under nitrogen for 48 hours. The reaction mixture is cooled to 0°, methanol is added, and the resulting solution is washed with water, dried (Na_2SO_4), and is concentrated. The residue is dissolved in methanol (6 ml) and 30 mg of 5% palladium on charcoal is added. The resulting mixture is stirred at −22° under 1 atmosphere of hydrogen for 4 hours. After filtration and concentration of the filtrate, the residue is stirred with a 65:35 mixture of acetic acid:water for 10 minutes at room temperature. The mixture is diluted with water, extracted with ethyl acetate, dried (Na_2SO_4) and concentrated to afford, after purification by silica gel chromatography, 9 - oxo - 11α,15α - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - trans - 13 - prostenoic acid.

EXAMPLE XX.

4 - (Tetrazol - 5 - yl)butyltriphenylphosphonium bromide

A mixture of 5 - bromovaleronitrile (16.2 g., 0.10 mole), triphenylphosphine (26.2 g., 0.10 mole) and toluene (100 ml.) was heated to reflux with stirring under nitrogen for 16 hours. The resulting thick white suspension was cooled to room temperature and filtered. The residue was washed with benzene and air dried to give 33.0 g. of a white, crystalline solid, m.p. 230—232°, which was 4 - cyanobutyltriphenylphosphonium bromide.

Anal. Calc'd for $C_{23}H_{23}BrNP$: C, 65.10; H, 5.47; N, 3.30.
Found: C, 65.01; H, 5.40; N, 3.19.

A mixture of the phosphonium salt above (10.0 g., 23.5 mmoles), ammonium chloride (1.60 g., 30.0 mmoles), lithium chloride (0.032 g., 0.76 mmole), sodium azide (1.91 g., 29.3 mmoles), and dimethylformamide (50 ml.) was heated to 127°

(oil bath) under nitrogen with stirring for 18 hours. The resulting suspension was cooled and filtered. The residue was washed with dimethylformamide and the combined filtrate and washings were concentrated (aspirator pressure, *ca.* 45°). The oily residue was crystallized from water at 0° and air dried to give a white crystalline solid (8.11 g.), m.p. 100—102°. The product was recrystallized from methanol-ether to give white prisms (7.18 g.). m.p. 197—206°. An analytical sample was prepared by recrystallization from 2-propanol to give a white crystalline powder, m.p. 212—213°, which was 4 - (tetrazol - 5 - yl)butyltriphenylphosphonium bromide.

Anal. Calc'd for $C_{23}H_{24}H_4PBr$: C, 59.10; H, 5.17; N, 11.99; P,6.63; Br, 17.09.

Found: C, 59.35; H, 5.28; N, 12.31; P, 6.78; Br, 17.26.

EXAMPLE XXI.

1 - (tetrazol - 5 - yl) - 9α - hydroxy - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadiene:

To a solution of 4 - (tetrazol - 5 - yl)butyltriphenylphosphonium bromide (1.49 gm) in a dry nitrogen atmosphere in 6.0 ml. dry DMSO is added 3.24 ml of a 2.0 M solution of sodium methylsulfinylmethide in DMSO. To this solution is added dropwise a solution of 615 mg 2 - [5α - hydroxy - 3α - (tetrahydropyran - 2 - yloxy) - 2β - (3α - tetrahydropyran - 2' - yloxy - 4 - phenoxy - *trans* - 1 butenyl)-cyclopent - 1α - yl]acetaldehyde, γ - hemiacetal in 5.0 ml dry DMSO over a period of 20 minutes. After an additional 2 hours stirring at room temperature the reaction mixture is poured onto ice water. The basic aqueous solution is acidified with 0.1N HCl and extracted with ethyl acetate. The residue obtained after evaporation of the solvent is chromatographed, to give pure 1 - (tetrazol - 5 - yl) - 9α - hydroxy - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadiene.

EXAMPLE XXII.

[4 - (methanesulfonylaminocarbonyl)butyl]triphenylphosphonium bromide

A mixture of 0.950 g. (0.01 mole) of methanesulfonamide and 1.80 g. (0.01 mole) of 5-bromovaleric acid chloride was heated on a steam bath until gas evolution ceased (*ca.* 5 minutes). The brown reaction mixture was allowed to cool and was dissolved in methylene chloride. The methylene chloride solution was treated with "Darco", was filtered, and was diluted with hexane with cooling to afford the white, crystalline *N*-methanesulfonyl-5-bromovaleramide weighing 2.22 g. (86.0% yield) which melted at 88—89°.

The nmr spectrum ($CDCl_3$) showed a broad singlet at 4.26—3.95 δ for the N—H, a multiplet at 3.66—3.23 for the —CH_2Br, a singlet at 3.31 δ for the SO_2—CH_3, a multiplet at 2.63—2.20 δ for the —CH_2CO, and a multiplet at 2.12—1.52 δ for the CH_2—CH_2. The ir spectrum ($CHCl_3$) showed a strong absorption at 1720 cm^{-1} attributable to the carbonyl group.

A solution of 2.20 g. (8.57 mmoles) of the *N*-methanesulfonyl-5-bromovaleramide, prepared as above, 2.24 g. (8.57 mmoles) of triphenylphosphine, and 20 ml. of acetonitrile was heated to reflux under nitrogen overnight. The solution was then concentrated by rotary evaporation and the resultant solid was triturated with hot benzene (4X). The triturated solid was recrystallized from absolute ethanol:ether to afford the white, crystalline [4-(methanesulfonylaminocarbonyl)butyl]triphenylphosphonium bromide weighing 2.80 g. (63.7% yield) melting at 190—191°.

The ir spectrum (KBr) of the product exhibited a strong absorption at 5.85 μ attributable to the carbonyl group. The nmr spectrum ($CDCl_3$) exhibited a complex multiplet at 8.14—7.27 δ for the aromatic protons, a multiplet at 4.00—3.30 δ for the —CH_2P, a singlet at 3.12 δ for the —SO_2CH_3, a multiplet at 3.00—2.38 δ for the CH_2CO, and a multiplet at 2.23—1.38 δ for the CH_2CH_2. A titration of the solid product indicated the pKa 1/2 to be 5.25.

EXAMPLE XXIII.

p - Biphenylyl 9 - oxo - 11α,15α - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoate:

To a solution of 50 mg (0.13 mmole) of 9 - oxo - 11α,15α - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoic acid and mg (0.4 mmole) of *p* - phenylphenol in 10 ml of dry methylene chloride was

added 825 mg (0.4 mmole) of *N,N'* - dicyclohexylcarbodiimide and the solution stirred overnight at room temperature. After concentration, the crude product was purified by silica gel chromatography to give the desired *p*-biphenylyl ester, m.p. 100—120°.

Anal.: Calc'd for $C_{36}H_{36}O_6$: C, 75.53; H, 6.71
Found: C, 75.65; H, 6.83.

EXAMPLE XXIV.

p - Biphenylyl 9α,11α,15α - trihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoate:

To a solution of 106 mg of 9α,11α,15α - trihydroxy - 16 - phenoxy - 17,18,19,20-tetranor - *cis* - 5 - *trans* - 13 - prostadienoic acid and 189 mg. of *p*-phenylphenol in 30 ml dry methylene chloride was added 600 mg of *N,N'*-dicyclohexylcarbodiimide and the solution stirred overnight at room temperature. After concentration, the crude product was purified by silica gel chromatography to give 80 mg pure *p*-biphenylyl ester, m.p. 101—103°.

Anal. Calc'd for $C_{34}H_{32}O_6$: C, 75.25; H, 7.06
Found: C, 75.38; H, 7.30.

EXAMPLE XXV.

1 - (Tetrazol - 5 - yl) - 9α,11α,15α - trihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadiene

A solution of 300 mg. 1 - (tetrazol - 5 - yl) - 9α - hydroxy - 11α,15α - *bis*(tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadiene in 6 ml. of 65:35 mixture of glacial acetic acid:water was stirred under nitrogen at 25° for 18 hours and then was concentrated by rotary evaporation. The resultant crude oil was purified by column chromatography on silica gel (Mallinckrodt CC-7, 100—200 mesh) using mixtures of chloroform:ethyl acetate as eluant. After elution of less polar impurities the colorless, oily 1 - (tetrazol - 5 - yl) - 9α,11α,15α - trihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadiene weighing 220 mg. (80% yield) was collected.

EXAMPLE XXVI.

1 - (Tetrazol - 5 - yl) - 9 - oxo - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadiene

To a solution cooled to –15° under nitrogen, of 600 mg. 1 - (tetrazol - 5 - yl) - 9α - hydroxy - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 *trans* -13 - prostadiene in 12 ml. reagent grade acetone was added dropwise 0.6 ml of Jones' reagent. After 30 minutes at –10°, 0.6 ml. 2 - propanol was added and the reaction mixture was allowed to stir an additional 5 minutes at which time it was combined with 75 ml. ethyl acetate, washed with water (3 x 10 ml.), dried (Na_2SO_4) and concentrated to give 510 mg. of the colorless, oily 1 - (tetrazol - 5 - yl) - 9 - oxo - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadiene.

EXAMPLE XXVII.

1 - (Tetrazol - 5 - yl) - 9 - oxo - 11α,15α - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadiene

A solution of 508 mg. 1 - (tetrazol - 5 - yl) - 9 - oxo - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadiene in 10 ml. of a 65:35 mixture of glacial acetic acid:water was stirred under nitrogen at 25° for 20 hours and then was concentrated by rotary evaporation. The resultant crude oil was purified by column chromatography on silica gel (Mallinckrodt CC-7 100—200 mesh) using mixtures of chloroform:ethyl acetate as eluants. After elution of less polar impurities the colorless oily 1 - (tetrazol - 5 - yl) - 9 - oxo - 11α,15α - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadiene weighing 240 mg. was obtained.

EXAMPLE XXVIII.

N - Methanesulfonyl - 9α - hydroxy - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadieneamide

To a solution of 1.7 g. [4 - methanesulfonylaminocarbonyl)butyl]triphenylphosphonium bromide in a dry nitrogen atmosphere in 6.0 ml. dry DMSO was added 3.2 ml. (6.5 mmole) of a 2.0 *M* solution of sodium methylsulfinylmethide in

DMSO. To this red ylid solution was added dropwise a solution of 610 mg. (1.29 mmole) 2 - [5α - hydroxy - 3α(tetrahydropyran - 2 - yloxy - 2β - (3α - tetrahydropyran - 2' - yloxy - 4 - phenoxy - *trans* - 1 - butenyl)cyclopent - 1α - yl]acetaldehyde, γ - hemiacetal in 5 ml. dry DMSO over a period of 20 minutes. After an additional 2 hour stirring at room temperature, the reaction mixture poured onto ice water. The basic aqueous solution was washed twice with ethyl acetate (3 x 20 ml.) and combined organic extracts washed once with water (10 ml.), dried (Na_2SO_4) and evaporated to an oil. Chromatography on silica gel afforded 684 mg. pure oily *N* - methanesulfonyl - 9*a* - hydroxy - 11α,15α - *bis*(tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide.

EXAMPLE XXIX.

N - Methanesulfonyl - 9α,11α,15α - trihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide

A solution of 250 mg. of *N* - methanesulfonyl - 9α - hydroxy - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide in 5 ml. of 65:35 mixture of glacial acetic acid:water was stirred under nitrogen at 25° for 18 hours and then was concentrated to a crude oil, which was purified by column chromatography on silica gel ("Mallinckrodt" CC-7, 100—200 mesh) using mixtures of chloroform:ethyl acetate as eluants. After elution of less polar impurities the colorless oily N-methanesulfonyl - 9α,11α,15α - trihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide weighing 180 mg. was collected. The product was shown to be homogeneous by liquid-liquid chromatography.

EXAMPLE XXX.

N - Methanesulfonyl - 9 - oxo - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide

To a solution cooled to −10° under nitrogen, of 400 mg. of *N* - methanesulfonyl - 9α - hydroxy - 11α,15α - bis - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide in 8 ml. reagent grade acetone was added dropwise 0.4 ml. of Jones reagent. After 30 minutes at −10°, 0.4 ml. 2 - propanol was added and the reaction mixture was allowed to stir an additional 5 minutes at which time it was combined with 60 ml. ethyl acetate, washed with water (3 x 10 ml.), dried (Na_2SO_4) and concentrated to afford 380 mg. of the colorless oily N - methanesulfonyl - 9 - oxo - 11α,15α - *bis* (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 *trans* - 13 - prostadienamide.

EXAMPLE XXXI.

N - Methanesulfonyl - 9 - oxo - 11α,15α - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide

A solution of 260 mg. of *N* - methanesulfonyl - 9 - oxo - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide in 6 ml. of a 65:35 mixture of glacial acetic acid:water was stirred under nitrogen at 25° for 20 hours and then was concentrated to a crude oil which was purified by column chromatography on silica gel (Mallinckrodt CC-7, 100—200 mesh) using mixtures of chloroform:ethyl acetate as eluants. After elution of less polar impurities the colorless N - methanesulfonyl - 9 - oxo - 11α,15α - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide weighing 130 mg. was obtained. The product crystallized from ether as colorless crystals, m.p. 76°.

EXAMPLE XXXII.

9β,11α,15α - Trihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoic acid

To a stirred solution of 0.18 g. (0.47 mmole) 9 - oxo - 11α,15α - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoic acid in MeOH (20 ml.) at 0° was added a cold solution of 0.06 g. $NaBH_4$ in MeOH (10 ml). After 1 hour at 0°, the reaction was quenched by addition of water (4 ml.) and concentrated under reduced pressure. The residue was acidified with 10% HCl to pH 3, extracted with ethyl acetate, dried (Na_2SO_4) and concentrated. Chromatography on 20 g. silica gel (CC-7) and elution with methanol-benzene afforded pure 9β,11α,15α - trihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoic acid, as a colorless oil, homogenous on t.l.c., R_f 0.25 (C_6H_6 - dioxan - HCO_2H, 15:5:2)

EXAMPLE XXXIII.

N - Benzoyl - 9 - oxo - 11α,15α - dihydroxy - 17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans* - 16 - phenoxy - prostadienamide:

To 1.0 m mole of 9 - oxo - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoic acid (Example VIII) in 40 ml. THF is added 2 ml. triethylamine. After 15 minutes of stirring at room temperature 10.0 ml of 0.1 molar benzoyl isocyanate in THF is added. After a further hour of stirring, the reaction mixture is neutralized with acetic acid and the solvent removed by evaporation *(in vacuo)*. The resultant residue is taken up in methylene chlorine and washed successively with water and sodium bicarbonate to yield, after drying and solvent evaporation, N - benzoyl - 9 - oxo - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide. This intermediate is then hydrolized overnight with acetic acid/water (as in Example IX) and purified by column chromatography to give the desired N - benzoyl - 9 - oxo - 11α,15α - dihydroxy - 5 - *cis* - 13 - *trans* - 16 - phenoxy - 17,18,19,20 - tetranorprostadienamide.

EXAMPLE XXXIV.

N - Methanesulfonyl 9 - oxo - 11α,15α - dihydroxy - 5 - *cis* - 13 - *trans* - 16 - phenoxy - 17,18,19,20 - tetranorprostadienamide:

To 1.0 m mole of 9 - oxo - 11α,15α - bis - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienoic acid (Example VIII) in 40 ml, THF is added 2 ml triethylamine. After 15 minutes of stirring at room temperature 10.0 ml of 0.1 molar methanesulfonyl isocyanate in THF is added. After a further hour of stirring, the reaction mixture is neutralized with acetic acid and the solvent removed by evaporation *(in vacuo)*. The resultant residue is taken up in methylene chlorine and washed successively with water and sodium bicarbonate to yield, after drying and solvent evaporation, *N* - methanesulfonyl - 9 - oxo - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* 5 - trans - 13 - prostadienamide. This intermediate is then hydrolized overnight with acetic acid/water (as in Example IX) and purified by column chromatography to give the desired *N* - methanesulfonyl - 9 - oxo - 11α,15α - dihydroxy - 5 - *cis* - 13 - *trans* - 16 - phenoxy - 17,18,19,20 - tetranorprostadienamide.

EXAMPLE XXXV.

N - Acetyl - 9α - hydroxy - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide

To a solution of 5.32 g [4 - (acetamidocarbonyl)butyl]triphenylphosphonium bromide in a dry nitrogen atmosphere in 10 ml dry DMSO was added 17.7 ml of a 2.0 *M* solution of sodium methylsulfinylmethide in DMSO. To this red ylid solution was added dropwise a solution of 0.524 g (1.1 mmoles) 2 - [5α - hydroxy - 3α - (tetrahydropyran - 2 - yloxy) - 2β - (3α - tetrahydropyran - 2' - yloxy - 4 - phenoxy - *trans* - 1 - butenyl)cyclopen - 1α - yl]acetaldehyde, γ - hemiacetal in 10 ml dry DMSO over a period of 20 minutes. After an additional 2 hours stirring at room temperature, the reaction mixture was poured onto ice water. The basic aqueous solution was washed twice with ethyl acetate (3 x 25 ml) and combined organic extracts washed once with water (10 ml), dried (Na_2SO_4) and evaporated to an oil. Chromatography on silica gel afforded 0.66 gm pure oily *N* - acetyl - 9α - hydroxy - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide.

EXAMPLE XXXVI.

N - Acetyl - 9α,11α,15α - trihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide

A solution of 0.39 g of *N* - acetyl - 9α - hydroxy - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide in 5 ml of 65:35 mixture of glacial acetic acid: water was stirred under nitrogen at 25° for 18 hours and then was concentrated to a crude oil, which was purified by column chromatography on silica gel (CC-7), using mixtures of chloroform:ethyl acetate as eluant. After elution of less polar impurities the colorless oil *N* - acetyl - 9α,11α,15α - trihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide weighing 95 mg. was collected.

EXAMPLE XXXVII.

N - Acetyl - 9 - oxo - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide:

To a solution cooled to −10° under nitrogen, of 394 mg *N* - acetyl - 9α - hydroxy - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide in 10 ml reagent - grade acetone was added dropwise 0.27 ml of Jones reagent. After 30 minutes at −10°, 0.4 ml 2-propanol was added and the reaction mixture was allowed to stir an additional 5 minutes at which time it was combined with 60 ml ethyl acetate, washed with water (3 × 10 ml), dried (Na_2SO_4) and concentrated to afford 390 mg of colorless oily *N* - acetyl 9 - oxo - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16- phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide.

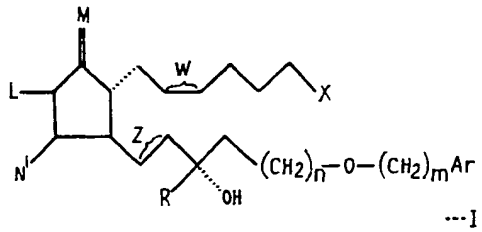
EXAMPLE XXXVIII.

N - Acetyl - 9 - oxo - 11α,15α - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide

A solution of 390 mg of *N* - acetyl - 9 - oxo - 11α,15α - *bis* - (tetrahydropyran - 2 - yloxy) - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide in 8 ml of a 65:35 mixture of glacial acetic acid:water was stirred under nitrogen at 25° for 20 hours and then was concentrated to a crude oil which was purified by column chromatography on silica gel using mixtures of chloroform ethyl acetate as eluants. After elution of less polar impurities the colorless oily *N* - acetyl - 9 - oxo - 11α,15α - dihydroxy - 16 - phenoxy - 17,18,19,20 - tetranor - *cis* - 5 - *trans* - 13 - prostadienamide weighing 76 mg.

WHAT WE CLAIM IS:—

1. An optically active or racemic compound of the formula:—



---I

and its C_{15} epimer;

wherein Ar is phenyl, 3,4-dimethoxyphenyl, 3,4-methylenedioxyphenyl, 3,4,5-trimethoxyphenyl; α- or β-naphthyl or monosubstituted phenyl wherein said substituent is halogen, trifluoromethyl, phenyl, lower alkyl or lower alkoxy; wherein lower is defined as 1 to 6 carbon atoms;

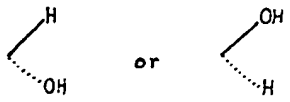
R is hydrogen or lower alkyl;

n and m are each O or integers from 1 to 3 with the proviso that the sum of n and m does not exceed 3;

W is a single bond or *cis* double bond;

Z is a single bond or *trans* double bond;

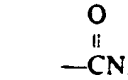
M is oxo,



N' and L when taken together form a single bond; or

N' is α-hydroxyl and L is hydrogen with the proviso that when N' and L together form a single bond M is oxo;

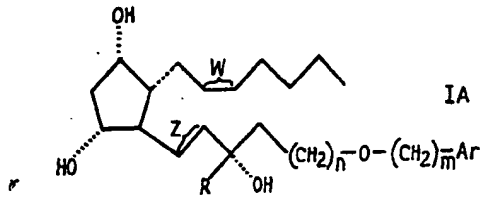
X is *p*-phenylphenoxycarbonyl; 5-tetrazolyl; or



wherein R" is alkanoyl having from 2 to 10 carbon atoms or cycloalkanoyl having from 4 to 8 carbon atoms; aroyl or substituted aroyl of from 7 to 11 carbon atoms

wherein said substituent is methyl, halogen, or methoxy; alkylsulfonyl of from 1 to 7 carbon atoms, arylsulfonyl or substituted arylsulfonyl wherein said substituent is methyl, halogen or methoxy; and the lower alkanoates, formates and benzoates of the hydroxy groups at the C_9-, C_{11}- and C_{15}-positions.

2. A compound according to claim 1, of the formula:—



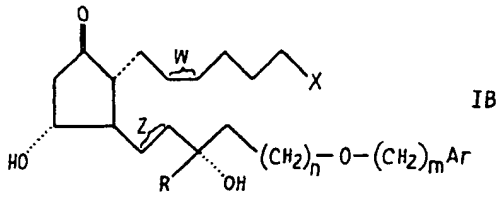
IA

and its C_{15} epimer, wherein Ar, R, m, n, W, Z and X are as defined in claim 1.

3. The compound of claim 1, wherein M is

L is a single bond and N' is α-hydroxyl and its C_{15} epimer.

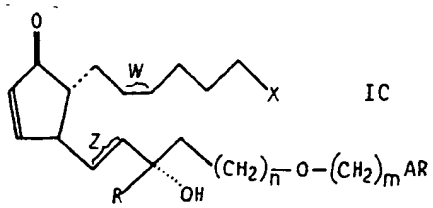
4. A compound according to claim 1, of the formula:—



IB

and its C_{15} epimer, wherein Ar, R, m, n, W, Z and X are as defined in claim 1.

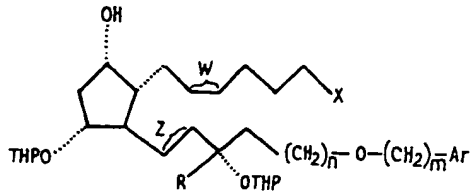
5. A compound according to claim 1, of the formula:—



IC

and its C_{15} epimer, wherein Ar, R, m, n, W, Z and X are as defined in claim 1.

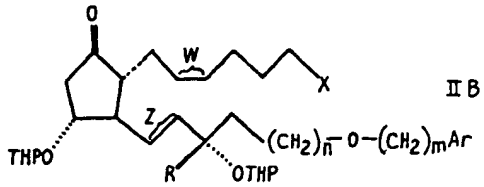
6. An optically active or racemic compound of the formula:—



IIAA

and the C_{15} epimer thereof; wherein Ar, R, m, n, W, Z, X and lower are as defined in claim 1; THP is 2-tetrahydropyranyl.

7. An optically active or racemic compound of the formula:—



IIB

and the C_{15} epimer thereof; wherein Ar, R, m, n, W, Z, X, lower and THP are as defined in claim 6.

8. The compound of claim 1, wherein n and m are each O, Ar is phenyl, W is a *cis* double bond, Z is a *trans* double bond, M is oxo, L is hydrogen and N' is α-hydroxy.

9. The compound of claim 1, wherein n and m are each O, Ar is phenyl, W is a *cis* double bond, Z is a *trans* double bond, M is

L is hydrogen and N' is α-hydroxy.

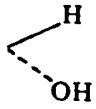
10. The compound of claim 1, wherein n is O, m is O, Ar is phenyl, W is a *cis* double bond, Z is a *trans* double bond, M is

L is hydrogen and N' is α-hydroxy.

11. The compound of claim 1, wherein n is O, m is O, Ar is phenyl, W is a *cis* double bond, Z is a *trans* double bond, M is oxo and N' and L together form a single bond.

12. The compound of claim 1, wherein n is O, m is 1, Ar is phenyl, W is a *cis* double bond, Z is a *trans* double bond, M is oxo, N' is α-hydroxy and L is hydrogen.

13. The compound of claim 1, wherein n is O, m is 1, Ar is phenyl, W is a *cis* double bond, Z is a *trans* double bond, M is



L is hydrogen and N' is α-hydroxy.

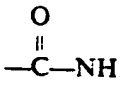
14. The compound of claim 2, wherein n and m are each O.

15. The compound of claim 2, wherein n and m are each 1.

16. The compound of claim 4, wherein n and m are each O.

17. The compound of claim 4, wherein n and m are each 1.

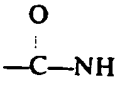
18. A compound according to claim 2, wherein X is



wherein R" is acetyl, W is a *cis* double bond, Z is a *trans* double bond, R is hydrogen, n and m are each O, Ar is phenyl.

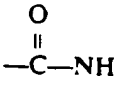
19. A compound according to claim 2, wherein X is 5-tetrazolyl, W is a *cis* double bond, Z is a *trans* double bond, R is hydrogen, n and m are each O, Ar is phenyl.

20. A compound according to claim 2, wherein X is



wherein R" is methanesulfonyl, W is a *cis* double bond, Z is a *trans* double bond, R is hydrogen, n and m are each O, Ar is phenyl.

21. A compound according to claim 2, wherein X is



wherein R″ is a methanefulfonyl, W is a *cis* double bond, Z is a *trans* double bond, R is hydrogen, n and m are each O and Ar is *m*-methoxyphenyl.

22. A compound according to claim 4, wherein X is

$$-C(=O)-NHR''$$

wherein R″ is acetyl, W is a *cis* double bond, Z is a *trans* double bond, R is hydrogen, n and m are each O, Ar is phenyl.

23. A compound according to claim 4, wherein X is

$$-C(=O)-NHR''$$

wherein R″ is acetyl, W is a *cis* double bond, Z is a *trans* double bond, R is hydrogen, n and m are each O and Ar is *m*-methoxyphenyl.

24. A compound according to claim 4, wherein X is tetrazolyl, W is a *cis* double bond, Z is a *trans* double bond, R is hydrogen, n and m are each O, Ar is phenyl.

25. A compound according to claim 4, wherein X is

$$-C(=O)-NHR''$$

wherein R″ is methanesulfonyl, W is a *cis* double bond, Z is a *trans* double bond, R is hydrogen, n and m are each O, Ar is phenyl.

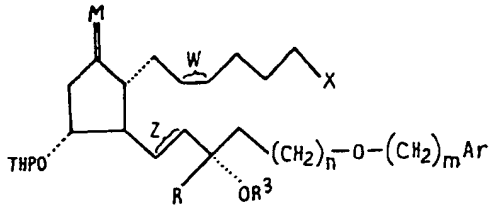
26. Optically active 16 - phenoxy - 17,18,19,20 - tetranor - PGE_2 *p*-biphenyl ester.

27. Optically active 16 - phenoxy - 17,18,19,20 - tetranor - $PGF_{2\alpha}$ *p*-biphenyl ester.

28. Optically active 16 - phenoxy - 17,18,19,20 - tetranor - $PGF_{2\beta}$ *p*-biphenyl ester.

29. A process for preparing a compound of formula I as claimed in claim 1, which comprises:—

a) when N′ is α-hydroxy and L is hydrogen and Ar, N, m, M, W, X and Z are as defined above, hydrolysing with an acid a compound of Formula IIC:—

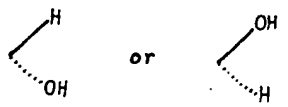


IIC

or the C_{15} epimer thereof, wherein Ar, n, m, W, Z and X are as defined above THP is 2-tetrahydropyranyl, and R^3 is hydrogen or THP, with the proviso that when R^3 is hydrogen M is oxo;

b) when N′ and L, when taken together form a single bond, M is oxo and Ar, n, m, R, W, X and Z are as defined above, reacting a compound of Formula I, above, wherein N′ is α-hydroxy and L is hydrogen, M is oxo and Ar, n, m, R, W, X and Z are as defined above, with an acidic dehydrating agent;

c) when N′ is α-hydroxy and L is hydrogen, M is



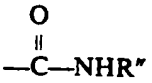
and Ar, n, R, W and Z are as defined above, reducing a compound of the Formula I, above, wherein N' is α-hydroxy and L is hydrogen, M is oxo, Ar, n, m, R, W, X and Z are as defined above, with a carbonyl reducing agent which does not react with ester or carboxamide groups or carbon to carbon double bonds, and, if desired, separating the 9α- and 9β-isomers;

d) when N' is α-hydroxy, L is hydrogen, Ar, R, n, m, M and X are as defined above, and W and Z are single bonds, catalytically hydrogenating a compound of Formula I, above, wherein Ar, R, n, m, M and X are as defined above, W is a single bond or *cis* double bond when Z is a *trans* double bond and Z is a single bond when W is a *cis* double bond;

e) when N' is α-hydroxy, L is hydrogen, Ar, R, n, m, X and M are as defined above, W is a single bond and Z is a *trans* double bond, selectively hydrogenating a compound of Formula I, wherein Ar, R, n, m, X and M are as defined above and W is a *cis* double bond and Z is a *trans* double bond;

f) when X is *p*-phenylphenoxycarbonyl, Ar, R, n, m, L, N', W and Z are as defined above, reacting a compound of Formula I wherein X is —COOH with *p*-phenylphenol;

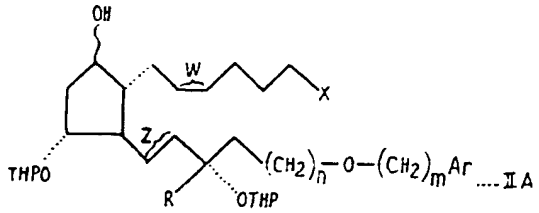
g) when X is



wherein R" is as defined above, M, Ar, R, n, m, L, N', W and Z are as defined above, reacting a compound of Formula I above wherein X is COOH with an isocyanate of the formula R"NCO, wherein R" is as defined above, and hydrolysing the compound thus obtained; and, if desired, preparing the 9α- or 9β-, 11α- and 15α lower alkanoates, formates or benzoates of the free hydroxy groups at the C_9, C_{11} and C_{15} positions by reacting said compounds with the appropriate acylating agents.

30. A process for preparing a compound of the formula IA as claimed in claim 2, which comprises:—

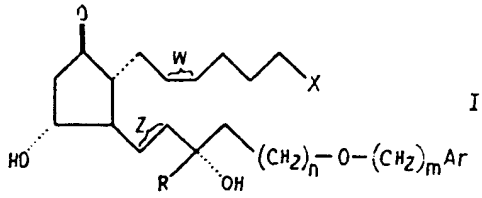
a) hydrolysing with an acid, a compound of Formula IIA:—



IIA

or its C_{15} epimer, wherein Ar, R, n, m, W, Z, X and THP are as hereinbefore defined;

b) reducing a compound of the formula:



IB

or its C_{15} epimer, wherein Ar, n, m, R, W, X and Z are as defined above, with a carbonyl reducing agent which does not react with ester or carboxamide groups or carbon to carbon double bonds, and then separating the 9α- and 9β-isomers;

c) catalytically hydrogenating a compound of Formula IA, above, wherein Ar, R, n, m and X are as defined above, W is a single bond or *cis* double bond when Z is a *trans* double bond and Z is a single bond when W is a *cis* double bond, to a compound of Formula IA, above, wherein Ar, n, M and X are as defined above and W and Z are single bonds;

d) when X is *p*-phenylphenoxycarbonyl, Ar, R, n, m, L, N', W and Z are as defined above, reacting a compound of formula I wherein X is —COOH with *p*-phenylphenol;

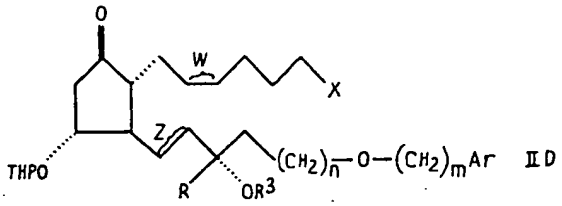
e) when X is

$$\begin{array}{c} O \\ \| \\ -C-NHR'' \end{array}$$

wherein R" is as defined above, M, Ar, R, n, m, L, N', W and Z are as defined above, reacting a compound of formula I above wherein X is COOH with an isocyanate of the formula R"NCO, wherein R" is as defined above, and hydrolysing the compound thus obtained; and, if desired, preparing the 9α- or 9β-, 11α- and 15α-tri(lower alkanoates), triformates or tribenzoates of the free hydroxy groups at the C_9, C_{11} and C_{15} positions by reacting said compounds with the appropriate acylating agents.

31. A process for preparing a compound of the formula IB as claimed in claim 4, which comprises:—

a) hydrolysing with an acid, a compound of Formula IID:—



IID

or its C_{15} epimer wherein Ar, R, m, n, W, Z, X, R^3 and THP are as defined above;

b) catalytically hydrogenating a compound of Formula IB, above, wherein Ar, X, R, m and n are as defined above W is a single bond or a *cis* double bond when Z is a *trans* double bond and Z is a single bond when W is a *cis* double bond, to afford a compound of Formula IB wherein Ar, X, m, n, and R are as defined above and W and Z are single bonds;

c) when X is *p*-phenylphenoxycarbonyl, Ar, R, n, m, L, N', W and Z are as defined above, reacting a compound of formula I wherein X is —COOH with *p*-phenylphenol;

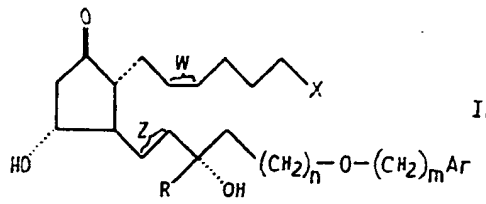
d) when X is

$$\begin{array}{c} O \\ \| \\ -C-NHR'' \end{array}$$

wherein R" is as defined above, M, Ar, R, n, m, L, N', W and Z are as defined above, reacting a compound of Formula I above, wherein X is COOH with an isocyanate of the formula R"NCO, wherein R" is as defined above, and hydrolysing the compound thus obtained, and, if desired, preparing the di(lower alkanoates), diformates or dibenzoates of the free 11- and 15-hydroxy groups by reacting said compounds with the appropriate acylating agents.

32. A process for preparing a compound of the formula IC as claimed in claim 5, which comprises:—

a) treating a compound of Formula IB:—

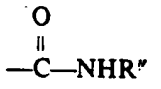


IB

or its C_{15} epimer wherein Ar, R, m, n, W, X and Z are as defined above, with an acid;

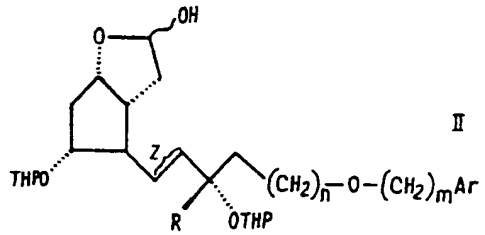
b) when X is *p*-phenylphenoxycarbonyl, Ar, R, n, L, N', W and Z are as defined above, reacting a compound of formula I wherein X is —COOH with *p*-phenylphenol;

c) when X is



wherein R" is as defined above, M, Ar, R, n, m, L, N', W and Z are as defined above, reacting a compound of formula I above, wherein X is COOH with an isocyanate of the formula R"NCO wherein R" is as defined above, and hydrolysing the compound, thus obtained; and, if desired, preparing the C_{15}-lower alkanoates, formates or benzoates by reacting said compound with the appropriate acylating agents.

33. A process for preparing a compound of the formula IIA as claimed in claim 6 which comprises reacting a compound of Formula II:—



II

or the C_{15} epimer thereof, wherein Ar, R, n, m, Z and THP are as defined above, with an ylide of the formula

$$(C_6H_5)_3P{=}CH{-}CH_2{-}CH_2{-}CH_2{-}X$$

wherein X is as defined above, with the proviso that when X is *p*-phenylphenoxycarbonyl, the compound of Formula II is first reacted with an ylide $(C_6H_5)_3$—P=CH—CH_2—CH_2—CH_2—CO_2H and the resulting compound esterified with *p*-phenylphenol, to afford a compound of Formula IIA wherein Ar, R, n, m, X, Z and THP are as defined above and W is a *cis* double bond, and, when required, subsequently hydrogenating a compound of Formula IIA above, wherein Ar, R, m, X, n and THP are as defined above, W is a *cis* double bond, and Z is a *trans* double bond, to form a compound of formula II above wherein Ar, R, m, n and THP are as defined above and W and Z are single bonds; selectively hydrogenating a compound of Formula IIA above wherein Ar, R, m, n and THP are as defined above, W is a *cis* double bond and Z is a *trans* double bond, to form a compound of Formula IIA, wherein Ar, R, m, X, n and THP are as defined above, W is a single bond and Z is a trans double bond.

34. A process for preparing a compound of the formula IIB as claimed in claim 7, which comprises reacting a compound of Formula IIA, as claimed in claim 6 with chromic acid in aqueous sulfuric acid and acetone.

35. Compounds of formula I as claimed in claim 1, substantially as hereinbefore described with reference to Examples XXI, XXIII, XXIV to XXXI and XXXIII to XXXVIII.

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